Manual for Procurement & Supply of Quality-Assured Maternal, Newborn and Child Health Commodities

UPDATED JUNE 2023

USAID
FROM THE AMERICAN PEOPLE

ACKNOWLEDGMENTS

This report was prepared by Wallada Im-Amornphong, Mark Laws, Alessandra Fleurent, Alessandra Tomazzini and reviewed by Lester Chinery at Concept Foundation. It is part of the project "Initiatives to Increase Supply of Quality-Assured Maternal and Child Health (MCH) Commodities," funded by the USAID Global Health Supply Chain, Procurement and Supply Management Project. The team is grateful to the late Ian Hayter for the research conducted in support of the manual. We would also like to give special thanks to Beth Yeager, Helen Petach, Debbie Armbruster, Lawrence Evans and PQM colleagues as USP for their invaluable contributions and feedback that steered the report.

TABLE OF CONTENTS

INTRODUCTION

The *Quality Assurance Manual for Procurement and Supply of Quality-Assured Maternal, Newborn and Child Health Commodities* is intended to assist national government procurement agencies in establishing a quality assurance system for procurement of maternal, newborn and child health (MNCH) products. It provides comprehensive information on specific quality requirements which must be met to ensure the quality, safety and efficacy of the MNCH products across the full supply chain up to the point of use by patients.

Procurement of quality-assured products is one of the most important steps in safeguarding patients' safety. The national government procurement agencies should develop and maintain a quality assurance system in accordance with the World Health Organization's (WHO) *Model Quality Assurance System for Procurement Agencies* (MQAS). [1,2]

The quality of any pharmaceutical product should be assessed against international norms and standards. In an ideal world, national government procurement agencies would want to rely on the WHO Prequalification (WHO PQ), Stringent Regulatory Authority (SRA) approval, or WHO's Expert Review Panel (ERP) recommendation to assure the quality of pharmaceutical products they procure. In reality, however, many MNCH products are not covered by the WHO PQ or ERP mechanism. While there may be SRA-approved MNCH products, many of these are only available in developed countries or be offered at uncompetitive price internationally.

Additionally, national medicine regulatory agencies (NMRAs) should have the capacity to ensure the quality, safety and efficacy of medicines however in some contexts, this can be challenging to achieve. Recognizing the need for standard system to support regulatory strengthening, WHO developed the Global Benchmarking Tool (GBT). The GBT is designed to assess regulatory frameworks and functions of a national regulatory system through standard indicators and scores the system in terms of maturity level, ranging from one to four. Maturity level 3 indicates a well-functioning regulatory system however in the absence or insufficiency of this standard, national government procurement agencies have two options to qualify the pharmaceutical products they want to procure:

- Relying on the evaluation conducted by the NMRA that does not meet a maturity level 3 on the GBT, which could be an indicator that the medicine regulation system operates below a standard level of stringency;

[1] World Health Organization. 2014. "Model Quality Assurance System for Procurement Agencies." Annex 3 in *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 48th Report. WHO Technical Report Series, No. 986. Geneva: WHO. Available at http://apps.who.int/medicinedocs/documents/s21492en/s21492en.pdf

[2] World Health Organization. 2014. "Assessment Tool Based on the Model Quality Assurance System for Procurement Agencies: Aide-Memoire for Inspection." Annex 4 in *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 48th Report. WHO Technical Report Series, No. 986. Geneva: WHO. Available at http://apps.who.int/medicinedocs/documents/s21468en/s21468en.pdf

- Setting up their own assessment procedures in line with international standards, which requires a level of resources and capacity that is unlikely to be available in low- and middle-income countries.

A pragmatic approach to assure the quality of MNCH products procured by resource-limited national government procurement agencies is therefore necessary to optimize the overall yield of existing mechanisms (WHO PQ, SRA approval, ERP recommendation, NMRA approval, internal assessment).[3] This involves using abridged assessment, including only recognized NMRAs, and applying different quality control requirements at pre-, post-shipment, and post-marketing surveillance. This should allow the resource-limited national government procurement agencies to access additional quality MCH products, beyond the WHO PQ, SRA, or ERP coverage.

In some countries, MNCH products are purchased through centralized public procurements typically managed by a country's central medical stores or by the authorized government procurement and supply division at the Ministry of Health. However, in many contexts, when medicines are not available in the public sector supply chain, health facilities purchase them directly from private wholesalers and retail pharmacies. For additional information, A Guide to Best Practices in Subnational Procurement of MNCH Commodities in the Public Sector provides best practices and case studies on procuring quality-assured, low-cost MNCH medicines and supplies in decentralized contexts.

In the long run, the goal should be building the capacity of national government procurement agencies in low- and middle-income countries to be able to prequalify the products they want to procure according to stringent standards. The NMRAs should also strengthen their own capacity and move toward the long-term goal of achieving GBT maturity level 3 status.

This manual is divided into 3 modules:

- **Module I** describes the general quality assurance for procurement as per the MQAS, including prequalification (selection) of pharmaceutical products and manufacturers; purchase of prequalified products; receipt and storage of purchased products; distribution of received products; and reassessment (monitoring) of pharmaceutical products and manufacturers.

- **Module II** sets out a pragmatic approach to assuring the quality of MNCH products that resource-limited national government procurement agencies may implement when assessing the products for prequalification and procurement.

- **Module III** provides useful technical information of life-saving MNCH products, including those listed by the UN Commission on Life-Saving Commodities for Women's and Children's Health (UNCoLSC), that national government procurement agencies can use to establish technical specifications for the product(s) to be prequalified.

[3] Moore, T., D. Lee, N. Konduri, and L. Kasonde. 2012. *Assuring the Quality of Essential Medicines Procured with Donor Funds. Health.* Nutrition and Population (HNP) discussion paper. Washington, DC: World Bank. World Health Organization. n.d

GLOSSARY

The definitions below apply to the terms used in this manual. They may have different meanings in other contexts.

ACTIVE PHARMACEUTICAL INGREDIENT (API): A substance or compound intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

BATCH RELEASE: The process performed by the manufacturer's quality assurance unit of releasing a batch or lot of active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) to the market based on a review of all manufacturing and control records to determine compliance with all established approved written procedures and specifications.

CERTIFICATE OF ANALYSIS (COA): The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether the sample complies with the specification.

CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP): A certificate issued for a single product in the format recommended by WHO, which establishes the status of the pharmaceutical product and that of the applicant for the certificate in the exporting country. It is issued by the competent authority in the exporting country in accordance with the requirements of the competent authority of the importing country.

COMMON TECHNICAL DOCUMENT (CTD): A common format for the submission of quality, safety, and efficacy information to regulatory authorities used in member countries of the the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and being adopted by other, non-member countries. The CTD is organized into five modules. Module 1 is region-specific, and Modules 2–5 are intended to be common for all regions. Module 1 is for administrative information and prescribing information. Module 2 contains the CTD summaries, including the overall summary of quality information, the non-clinical overview and summary, and the clinical overview and summary. As a foundation for the CTD summaries, Module 3 contains detailed information on quality topics, Module 4 contains the non-clinical study reports, and Module 5 contains the clinical study reports.

COMPARATOR PRODUCT: A pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product, for which efficacy, safety, and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle as described in Guidance on the Selection of Comparator Pharmaceutical Products Equivalence Assessment of Interchangeable Multisource (Generic) Products (WHO Technical Report Series, No. 992, Annex 8 [2015]) should be used to identify a suitable alternative comparator product.

COMPLAINT HANDLING: A process of receiving, recording, investigating, and implementing appropriate corrective and preventive actions for any complaints and other

information concerning potentially defective products received by a company according to GMP.

CONTRACT MANUFACTURER: A manufacturer performing some aspect of manufacturing on behalf of the primary manufacturer.

DISTRIBUTION: The procuring, purchasing, holding, storing, selling, supplying, import, export, or movement of pharmaceutical products, with the exception of the dispensing or provision of pharmaceutical products directly to a patient or his or her agent.

EXPERT REVIEW PANEL (ERP): The ERP is an independent advisory body of technical experts, coordinated by WHO. The ERP is a service to procurement or funding agencies. The ERP assesses the quality risks of pharmaceutical products that do not yet meet all stringent quality requirements, and based on transparent science-based criteria, provides advice for the purpose of aiding decisions regarding time-limited procurement.

FALSIFIED MEDICINES: Pharmaceutical products that deliberately/fraudulently misrepresent their identity, composition, or source.

FINISHED PHARMACEUTICAL PRODUCT (FPP): A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labeling.

GOOD DISTRIBUTION PRACTICES (GDP): That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities that occur during distribution as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.

GOOD MANUFACTURING PRACTICES (GMP, ALSO REFERRED TO AS *cGMP,* OR *CURRENT GOOD MANUFACTURING PRACTICE*): That part of quality assurance that ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization.

GOOD STORAGE PRACTICES (GSP): That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage.

INNOVATOR PRODUCT: Generally, the pharmaceutical product that was first authorized for marketing (typically as a patented product) on the basis of documentation of efficacy, safety, and quality.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH): An initiative involving regulatory bodies and pharmaceutical industry experts in the United States, Europe, and Japan that was established to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration to ensure that safe, effective, and quality-assured medicines are developed and registered in the most resource-efficient manner.

INVITATION FOR EXPRESSION OF INTEREST (EOI): Invitation calling upon interested parties (e.g., manufacturers or other suppliers) to submit an expression of interest (EOI) to the procurement agency by a specified deadline, for the purpose of participating in the

prequalification procedure for specified product(s). An EOI should be accompanied by the required information on the relevant product(s).

MANUFACTURE: All operations of purchase of materials and products for production, quality control, release, storage, and distribution of pharmaceutical products, as well as the related controls.

MANUFACTURER: A company that carries out operations such as production, packaging, repackaging, labeling, and re-labeling of pharmaceuticals.

MARKETING AUTHORIZATION: Also referred to as product license or registration certificate. A legal document issued by a medicines regulatory authority that authorizes the marketing or free distribution of a medical product in the respective country after evaluation of its safety, efficacy, and quality. In terms of quality, it establishes the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labeling, storage conditions, shelf-life, and approved conditions of use.

NATIONAL MEDICINE REGULATORY AUTHORITY (NMRA): A national body that administers the full spectrum of medicine regulatory activities, including, at a minimum, all of the following functions, in conformity with national medicine legislation:

- Marketing authorization of new products and variations of existing products
- Good Manufacturing Practices (GMP) inspection
- Inspection and licensing of manufacturers, wholesalers, and distributors
- Quality control laboratory testing
- Monitoring of adverse drug events (pharmacovigilance)
- Control of clinical trials
- Post-marketing surveillance of medical products' quality
- Provision of information on medicines and promotion of rational use of medicines
- Enforcement operations

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S): A non-binding, informal cooperative arrangement between regulatory authorities in the field of Good Manufacturing Practices (GMP) for medicinal products for human or veterinary use. It is open to any authority having a rigorous GMP inspection system. PIC/S aims at harmonizing inspection procedures worldwide by developing common standards in the field of GMP and providing training opportunities to inspectors. It also aims at facilitating co-operation and networking between competent authorities and regional and international organizations, thus enhancing mutual confidence.

PHARMACEUTICAL PRODUCT: Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in humans, or with a view to making a medical diagnosis in humans, or to restoring, correcting, or modifying physiological functions in human.

PHARMACOVIGILANCE: The science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.

PREQUALIFICATION: The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the

product or service offered against the specification and the facility where the product or service is prepared against common standards of Good Manufacturing Practices (GMP). The inspection of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors according to common accepted standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the decision. Prequalification is required for all pharmaceutical products to be procured, regardless of their composition and place of manufacture/registration, but the extent and type of information requested from the supplier for assessment by the procurement agency may differ.

PROCUREMENT: The process of purchasing or otherwise acquiring any pharmaceutical product. For the purpose of this manual, *procurement* means the preselection of products and manufacturers through a procedure of qualification, including *prequalification* (see above) and continuous monitoring of these thereafter, purchase of the prequalified products from prequalified manufacturers (linked to the specific product) through defined purchasing mechanisms, storage and distribution.

PROCUREMENT AGENCY: A procurement agency, in the context of this manual, is defined as any organization, including national government procurement agency, purchasing pharmaceutical products or otherwise involved in their *prequalification* (see above), purchasing, storage, and distribution of pharmaceutical products.

PRODUCT INFORMATION PACKAGE: Information on pharmaceutical products submitted by manufacturers or suppliers in any of the formats specified in the procurement agency's guidelines to obtain prequalification for the products.

PRODUCT QUALITY REVIEW: Regular periodic or rolling quality reviews of all authorized medicinal products, including export-only products, which is conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify needed product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews. Product quality review is a GMP requirement listed under Chapter 1, Pharmaceutical Quality System, of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) GMP Guideline.

PRODUCT RECALL: A process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse events related to the product, and/or concerns that the product is or may be falsified. The recall might be initiated by the manufacturer, importer, wholesaler, distributor, or a responsible agency.

QUALITY ASSURANCE: Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

QUALITY CONTROL: Quality control is concerned with sampling, specifications, and testing, and with the procurement agency's documentation and acceptance/rejection procedures that ensure that the necessary and relevant tests are carried out and that starting materials, intermediates, and finished products are not accepted for use, sale, or supply until their quality has been judged satisfactory.

RECALL: A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall may be initiated by the manufacturer/importer/distributor or a responsible agency.

SHELF LIFE: The period of time during which a pharmaceutical product, if stored as indicated on the label, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf life is used to establish the expiry date of each batch.

SPECIFICATIONS: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the product described. It establishes the set of criteria to which a material must conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

STRINGENT REGULATORY AUTHORITY (SRA): A regulatory authority that is one of the following:

a) A member of the International Conference on Harmonisation (ICH) effective prior to October 23, 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan, including its Pharmaceuticals and Medical Devices Agency

b) An ICH observer effective prior to October 23, 2015, namely: the European Free Trade Association, as represented by Swissmedic, and Health Canada

c) A regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement effective prior to October 23, 2015, namely: Australia, Iceland, Liechtenstein, and Norway

SUBSTANDARD MEDICINES: Substandard medicines are pharmaceutical products that fail to meet either their quality standards or their specifications, or both. Each pharmaceutical product that a manufacturer produces must comply with quality assurance standards and specifications, at release and throughout its shelf life, according to the requirements of the territory of use. Normally, these standards and specifications are reviewed, assessed, and approved by the applicable national or regional medicines regulatory authority before the product is authorized for marketing.

SUPPLIER: A person or entity providing pharmaceutical products and materials on request. Suppliers may be agents, brokers, distributors, manufacturers, or traders. Where possible, suppliers should be authorized by a competent authority.

UNREGISTERED MEDICINES: Pharmaceutical products that have not undergone evaluation and/or approval by the national or regional medicine regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

VARIATION: A change to any aspect of a pharmaceutical product, including but not limited to: the change of use of a starting material; a change to formulation, method, or site of manufacture; or change to specifications for the finished product and ingredients, container, and container labeling and product information. Variations can be classified as follows:

- Major variations are changes that could have major effects on the overall safety, efficacy, and quality of the finished pharmaceutical product (FPP). Manufacturers must submit the supporting data requiring the changes to the regulatory

authority. Prior acceptance by the regulatory authority is required before the changes can be implemented.

- Minor variations are changes that may have minor effects on the overall safety, efficacy, and quality of the FPP. Manufacturers must meet all of the prescribed conditions for the change and submit the required documentation to the regulatory authority. Such minor variations can be implemented if no objection letter has been issued within a time period indicated by the regulatory authority. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from the regulatory authority.
- Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy, and quality of the FPP. Such notifications do not require prior acceptance but must be documented in notification to the regulatory authority immediately after implementation (immediate notification), or within 12 months following implementation (annual notification), depending on the types of changes, as indicated by the regulatory authority.

MODULE I

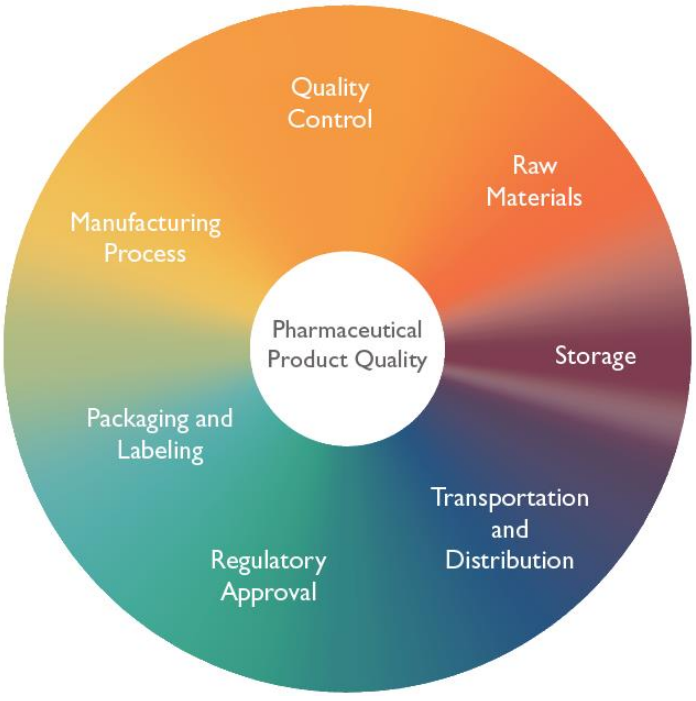
QUALITY ASSURANCE IN PROCUREMENT

MODULE I

QUALITY ASSURANCE IN PROCUREMENT

Quality assurance (QA) is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates several factors and it is an integral part of all key activities in the product supply chain (Figure 1).

Figure 1: Determinants of pharmaceutical product quality in the supply chain



The determinants of pharmaceutical product quality in the supply chain and corresponding quality assurance approaches can be outlined as follows.

Raw materials

The quality of raw materials used to manufacture the product is critical in determining the quality of the finished pharmaceutical product. Therefore, sources and quality of the raw materials (active and inactive ingredients) must be assessed to ensure that they meet regulatory and international quality standards.

Quality control

The finished pharmaceutical product (FPP) must pass internal quality control testing performed by the manufacturer prior to submission for registration. Subsequently, once the product is approved, every lot released to the market must have a Certificate of Analysis (COA). In addition, once the manufacturer has been selected for procurement, the pharmaceutical product must pass the random pre- and post-shipment inspections conducted by the procurement agency through an independent inspecting agent using an independent WHO-prequalified or ISO:IEC 17025 certified quality control laboratory. Pre- and post-shipment testing assures the pharmaceutical product complies with the standards applied by the procurement agency and its regulatory requirements.

Manufacturing process

The manufacturing site and process used for the pharmaceutical product must comply with current Good Manufacturing Practice (cGMP) requirements, as evidenced by GMP certificate and/or inspection report issued by the WHO Prequalification Team: Medicines (PQTm), an SRA, a Pharmaceutical Inspection Co-operation Scheme (PIC/S) member inspectorate, or a recognized NMRA or regional registration harmonization initiative.

Packaging and labeling

The packaging components should be suitable with respect to safety of materials, compatibility of the materials with the finished product, and protection from moisture and light, to ensure product quality during transportation and storage. Labels and product information for health care providers and end users should be provided in the appropriate format and comply with the regulatory requirements of the country where the product will be used. Labels should contain information on cold storage if the product is heat-sensitive.

Regulatory approval

The pharmaceutical product should obtain regulatory approvals from the NMRA in the country of origin and the country where it will be used, proving that the product meets acceptable standards of safety, efficacy, and quality. Furthermore, regulatory approval from any SRA, WHO prequalification, and recommendation for procurement from ERP are good indicators that the pharmaceutical product is of assured quality, safety, and efficacy.

Transportation and distribution

The pharmaceutical product should be transported and distributed in a manner that will maintain the appropriate storage conditions (e.g., controlled temperature, protection from

the environment). The logistics system should support and ensure access and availability for these processes without compromising quality.

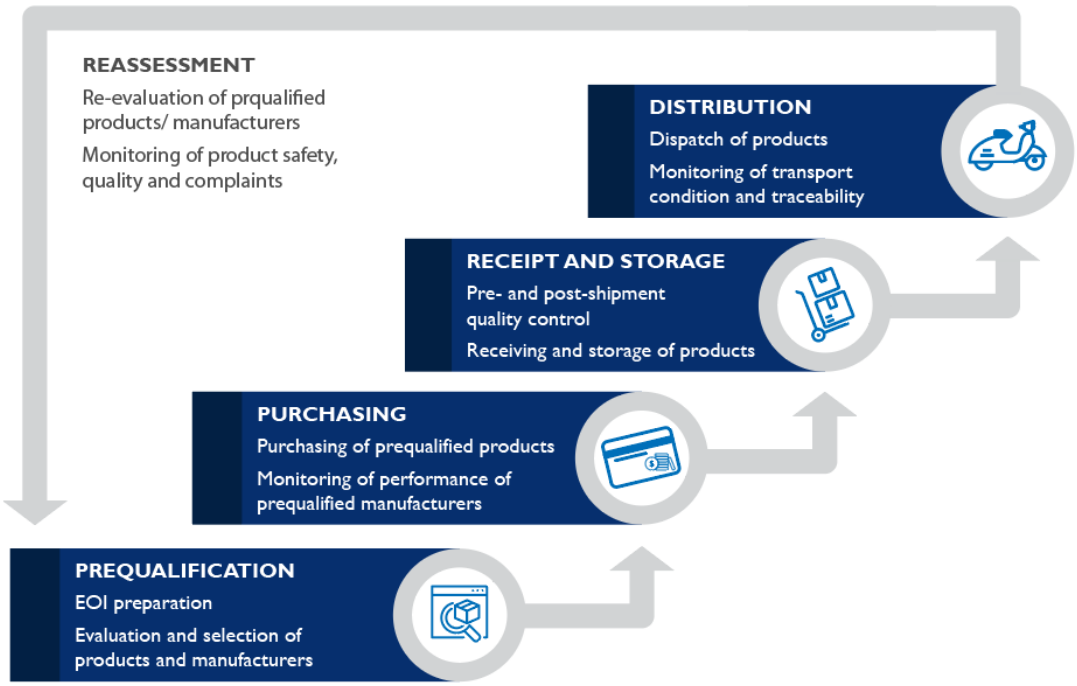
Storage

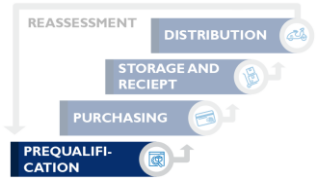
The pharmaceutical product needs to be stored under the appropriate conditions established based on the results of stability testing, in order to avoid changes in quality that may affect the safety and/or efficacy of the final product to be administered to/consumed by the public. Where special storage conditions are required (e.g., cold chain) these should be provided, checked, monitored, and records maintained.

According to WHO's MQAS, in the procurement of pharmaceutical products, quality assurance covers all steps in the provision of these products, as shown in Figure 2. The key objective of quality assurance during procurement is to ensure that only pharmaceutical products that are safe, effective, and of assured quality, and conform with internationally recognized standards for pharmaceutical products, are procured and *that their quality is maintained* until supplied to end users.

The quality assurance approaches for each step in the procurement of pharmaceutical products (as shown in Figure 2) will support procurement agencies in ensuring that procurement is carried out in accordance with the WHO MQAS. Ensuring an effective quality assurance system during procurement will reduce risks of sourcing substandard or falsified pharmaceutical products and reduce the risk of subsequent deterioration, thereby potentially reducing the incidence of product complaints and recalls, financial losses, and most important, the risk of harming patients' health.

Figure 2: Quality assurance framework for the procurement of pharmaceutical products





PREQUALIFICATION

Prequalification is one of the key elements in ensuring purchase and supply of quality-assured pharmaceutical products. Prequalification includes the activities undertaken in defining a product need, seeking expressions of interest (EOI) from manufacturers to supply the product, and assessing the product offered against the specifications, and assessing the facility where the product is manufactured against cGMP standards.

The list of prequalified products from a specific manufacturing site is identified following the product evaluation and manufacturing site inspection. Maintaining a list of prequalified products ensures that quality products are obtained from qualified sources.

The procurement agency should have trained and qualified personnel to perform prequalification activities as described in the WHO MQAS. The procurement agency should establish a document describing the policy and procedures for prequalification, including standards and criteria used in the evaluation of product information and manufacturing facilities. Prequalification requires a knowledge of QA principles, and the prequalification staff make decisions regarding quality.

Where prequalification activity is delegated to another organization (e.g., expert review panel, external evaluators, or quality control laboratory), a written agreement is required between the two parties. The contract giver should ensure that the contract acceptor meets the required qualifications. The written agreement for the performance of work and terms of reference for contracted evaluators should be in place before commencement of work.

Key Steps in the Prequalification Process

Figure 3 summarizes the key steps in the prequalification process. The quality assurance approaches for each step in the prequalification process are described below.

Figure 3: Prequalification process

STEP 01

Solicit information

Prepare expression of interest, including product specification
Establish submission procedures

Develop a list of product specifications

The procurement agency should develop a list or catalog of products, described by International Nonproprietary Name (INN), that are identified for purchasing based on need, the national list of essential medicines, and the *WHO Model List of Essential Medicines.*[1] The unit or appointed person responsible for prequalification should establish technical specifications for the product(s) to be prequalified. The specifications should be detailed, clear, and unambiguous to avoid unnecessary submission and processing of documentation not relevant to the product to be sourced.

The product specifications should state, at a minimum:

- Name of the active pharmaceutical ingredient (API)/INN
- Strength per dose
- Dosage form (route of administration)
- Primary packaging materials
- Pack size
- Shelf life
- Labeling requirements

Recommended technical specifications for key MNCH products are provided in Module III of this manual.

Moreover, to be eligible for procurement and supply, the product also requires approval by the NMRA in both the country of origin and the country where it will be used.

Establish quantification

All requests for products should include quantities. The personnel responsible for purchasing should establish quantification. Accurate quantification (forecast and supply plan) of needs is essential to avoid shortages or excess stocks. Quantities purchased should be based on a reliable estimate of actual need. The possible methods of product quantification include the consumption method, the morbidity method, and the adjusted or extrapolated consumption method, or better, a combination of several methods. Guidance on quantification of MNCH products should be consulted.[2,3]

---

[1] World Health Organization. n.d. *WHO Model List of Essential Medicines.* Geneva: WHO. Available at http://www.who.int/medicines/publications/essentialmedicines/en/

[2] JSI and SIAPS. 2015. Quantification of Health Commodities: RMNCH Supplement Forecasting Consumption of Select Reproductive, Maternal, Newborn and Child Health Commodities. Updated January 2016. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health. Submitted to the United Nations Children's Fund by JSI. Arlington, VA: JSI Research & Training Institute, Inc. Available at http://apps.who.int/medicinedocs/documents/s22288en/s22288en.pdf

[3] USAID | DELIVER PROJECT. 2014. *Quantification of Health Commodities: A Guide to Forecasting and Supply Planning for Procurement.* Arlington, VA: USAID | DELIVER PROJECT, Task Order 4. Available at http://apps.who.int/medicinedocs/documents/s21547en/s21547en.pdf

Define procurement method

The procurement agency should apply the procurement method according to their policy and procedures. There are different methods of procurement. A brief description of each procurement method is provided below.

- **Restricted tender**
  In a restricted tender, also called a "closed bid" or "selective tender," interested suppliers are approved in advance through a prequalification process. This type of procurement is often referred to as *limited international bidding* (LIB), which is an "invitation to competitive bids" conducted by direct invitation to all prequalified suppliers. Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health products and services whenever possible.

- **Competitive negotiation**
  This method is also referred to as "international/national shopping." The basis of this method is the comparison of price quotations obtained from several local or foreign suppliers. Usually, quotations are solicited from a minimum of three suppliers to ensure competitive prices. This method is appropriate for procuring small amounts of readily available products. However, its use should be explicitly justified, and approval should be obtained from senior management. Only prequalified products and suppliers should be used.

- **Direct procurement**
  In direct procurement, products are obtained directly from a single source without applying the requirements of a tender process or comparing price quotations. Normally, direct procurement is not recommended, but it may be used when there is only one prequalified source for the product to be procured. A history of "reasonable" prices for the product in question should be assessed to negotiate the price with the supplier.

- **Open tender**
  Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of goods. The term *international competitive bidding* (ICB), which is an open tender to all manufacturers, is often used. Open tendering is not appropriate for health products because it may be difficult to establish, before a contract is awarded, whether unknown bidders will be able to supply products of the required quality in the required quantities on a sustained basis.

Establish procedure of submission and content of product information package

The unit or appointed person responsible for prequalification should establish the procedure for submitting product information package. The procedure should be written in clear, unambiguous language and should contain information detailing, at a minimum:

- The content (i.e., type of product information required) and format of submission (i.e., paper or electronic submission)

- The process of submission, including the focal point for the submission and address to which the documentation should be sent

The type of product information required for submission will depend on the registration status of products to be prequalified. According to the WHO MQAS, the product information package may be in three different formats:

- For products manufactured and registered in countries where regulatory requirements are in line with international regulations for assessment of safety, efficacy, and quality, the following information should be submitted:
  - A WHO-type certificate of pharmaceutical product (CPP) issued by a stringent regulatory authority, together with a Summary of Product Characteristics (SmPC), or proof of the official registration of the product.
  - If the product is different from the one registered by the SRA, arguments and/or data to support the application should be submitted. These may include differences in formulation, strength, or other specifications, such as packaging.
  - Products that are registered for export purposes only should be fully assessed unless these were approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Article 58 of European Union Regulation (EC) No. 726/2004 or US Food and Drug Administration (US FDA) tentative approval.
- A standard product dossier as prepared for an NMRA should be submitted, provided it contains the appropriate information as required in the WHO guidelines (e.g., common technical document [CTD]). In such cases, the supplier should provide a covering letter that indicates where the required information can be found in the standard product dossier.
- A completed pharmaceutical product questionnaire with supporting information as listed in the annexes should be submitted. The interagency finished pharmaceutical product questionnaire is shown in Appendix 6 of the WHO MQAS.

It is apparent that, in the absence of WHO-prequalified or SRA-approved products, the procurement agency needs to review the product dossier or product questionnaires (options 2 or 3 above) submitted by the manufacturer to prequalify the product to be purchased. In reality, however, many procurement agencies have limited capacity or lack the technical expertise to do so. A pragmatic approach, using different assessment processes, documentation requirements, and quality control requirements, depending on the registration status of the product (e.g., WHO prequalification, SRA approval, ERP recommendation, recognized NMRA approval), is therefore suggested. Details can be found in Module II.

Prepare and publish the invitation for EOI

Once the product specifications, quantification, procurement method, content of product information package, and procedure for submission are established, the invitation for EOI can be published widely to the manufacturers. The information in the EOI should include, at a minimum:

- Purpose of the invitation
- List of products, including specifications for each product
- Information on quantities required
- Details of the information to be submitted
- Procedure for submission, including information on details to be submitted, on the focal point for submission and on the format for submission

- Contact details (name, address, telephone number, fax, email, and postal address) for submission
- The closing date for receipt of the information by the procurement agency

An sample EOI is provided in Appendix 5 of the WHO MQAS.

STEP 02

Receive product information

Identify, mark, and record the received files and samples
Allocate the unique reference number

The procurement agency should have the necessary infrastructure to receive and process the product information package submitted by manufacturers. It will require personnel for processing the documentation; written procedures for receiving, identifying, and marking files, containers, and samples; and sufficient space for unpacking and storage.

Each product should be allocated a unique reference number to ensure traceability of the product information package. A record of all the information received from each manufacturer should be maintained.

STEP 03

Screen product information

Check completeness of the product information package received and put in record
Inform the manufacturer the screening results and/or request for missing information

Each product information package submitted by the manufacturer should be screened for completeness. The screening should be done in accordance with a written procedure. A screening form should be used to ensure consistency of screening. There should be a written record of the screening of each product information package. Information to be recorded should include:

- Date of receipt
- Product number
- Name of product
- Name of the applicant (i.e., supplier)
- Name and address of manufacturer
- Outcome of screening

An example of a standard operating procedure (SOP) for screening, including a sample screening form, is shown in Appendix 7 of the WHO MQAS.

Only product information packages that meet the requirements of the screening procedure should be retained for full evaluation. Incomplete product information packages should be excluded from the evaluation procedure and inspection process. The manufacturer should be informed of an incomplete information package and requested to supply the missing information within a specified period. If this request is not complied with, the application should be rejected on grounds of incompleteness.

STEP 04

Step 4: Evaluate product information

Abbreviated assessment for products with WHO prequalification, SRA approval, ERP recommendation, or recognized NMRA approval
Otherwise, full assessment

The personnel responsible for evaluation of the product information package should have relevant qualifications and experience, which may include a background in pharmaceuticals, pharmaceutical chemistry, or pharmacology. Ideally, they should be from a pharmaceutical regulatory background or have regulatory experience.

Suitably qualified external evaluators may be appointed, subject to compliance with the policy of the procurement agency regarding aspects such as confidentiality, conflicts of interest, and financial resources.

Different assessment approaches may be used, depending on the registration status of products to be prequalified. For example, full assessment may not be required, and an abridged assessment may be used instead, when products are already prequalified by the WHO PQTm, approved by an SRA, or recommended for use by the ERP. Details are given in Module II of this manual.

Time frames should be set for evaluation of the product information package. A written procedure for evaluation should be followed. A sample SOP for evaluating the product information package is shown in Appendix 7 of the WHO MQAS. The person responsible for evaluation should monitor the process to ensure that each product information package is evaluated in compliance with these requirements.

Each evaluator should prepare a formal evaluation report for each product, including a recommendation for acceptance or rejection. The evaluation report should be communicated to the manufacturer.

A response should be invited from the manufacturer in cases where data and information are found to be incomplete or do not meet the guidelines. A reasonable period should be allowed for submission of additional data and information. This additional information should be assessed, and the final outcome of the evaluation should be communicated to the manufacturer.

The evaluation report should be filed with the product evaluation documentation for reference purposes and follow-up where relevant.

Samples may be analyzed—if deemed necessary based on risk assessment—in accordance with the finished product specification. If deemed necessary, samples should be randomly selected for analysis. Certificates of analysis of product samples should be made available to the procurement agency.

The procurement agency should have access to a quality control laboratory to perform analyses. Alternatively, a laboratory may be contracted to perform the analyses. In either case, the procurement agency should ensure that the laboratory complies with cGMP and Good Laboratory Practices (GLP).[4] The use of a WHO-prequalified quality control

[4] World Health Organization. 2010. "WHO Good Practices for Pharmaceutical Control Laboratories." Annex 1 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 44th Report. WHO Technical Report Series, No. 957. Geneva: WHO. Available at http://apps.who.int/medicinedocs/documents/s18681en/s18681en.pdf

laboratory or an ISO:IEC 17025 accredited laboratory is therefore recommended. The list of WHO-prequalified quality control laboratories can be found at https://extranet.who.int/prequal/content/medicines-quality-control-laboratories-list.

The procurement agency is responsible for ensuring access to raw data. The procurement agency should have a procedure for investigating, handling, and reporting out-of-specification results when these are obtained from laboratories. If a sample fails to meet the specifications, the procurement agency should investigate the problem and communicate the outcome to the manufacturer.

Step 5: Perform inspection

Desk review of GMP evidences from the WHO PQP, an SRA, a PIC/S member inspectorate, or a competent NMRA
Preform GMP inspection if deemed necessary

The need for an inspection may be waived where there is evidence that the site was inspected and approved by the WHO PQTm, an SRA, a PIC/S member inspectorate, a recognized NMRA, or regional registration harmonization initiative, if the following conditions apply:

- All aspects of cGMP for the relevant product(s) have been covered.
- The approval was within the last 36 months.
- There is a statement from the manufacturer that no major changes have been made to the premises, equipment, or key personnel since the inspection by the WHO PQTm, SRA, PIC/S member inspectorate, recognized NMRA, or regional registration harmonization initiative.

In addition to the GMP certificate, a copy of the inspection report, corrective and preventive action (CAPA) reports, and the most recently completed product quality review report from the manufacturer may be requested to verify the cGMP compliance status of the manufacturing site as part of the prequalification procedure.

However, GMP inspection may be warranted under certain circumstances—for example, report of incidents with the product and/or manufacturer. Inspections should be performed in accordance with a written procedure.

Information submitted in relation to the supply of the API, formulation of the product, manufacturing method, and stability data should be verified during the inspection. The inspection should cover the evaluation and assessment of the manufacturing documentation, premises, equipment, utilities, and materials. It should also cover verification of data and documentation, such as results, batch records, compliance with an SOP, as well as information submitted on the manufacturing method, equipment. Inspection should further include (but not be limited to) validation of the manufacturing process, validation of utilities and support systems, and validation of equipment.

Personnel responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, cGMP and GDP, performing inspections and audits, chemistry, and quality control. Ideally, they should have an inspection background from working with a pharmaceutical regulatory authority or experience in managing manufacturing sites. A sufficient number of inspectors should be appointed to carry out inspections within predetermined time frames. External inspectors

may be appointed, provided there is no conflict of interest and confidentiality undertakings are agreed upon and maintained.

The inspector or inspection team should prepare a formal inspection report for each manufacturing site inspected, and make a recommendation on the status of the manufacturer in relation to compliance with cGMP. The inspection report should be communicated to the manufacturer. Where non-compliance was observed, corrective actions and timelines for completing them should be suggested. A response with supporting documentation should be invited from the manufacturer. If any additional information is required, or if corrective action is necessary, a final recommendation as to the acceptability of the product and manufacturer should be made only after such information has been evaluated or the corrective action has been verified.

STEP 06

Step 6: Finalize the assessment process

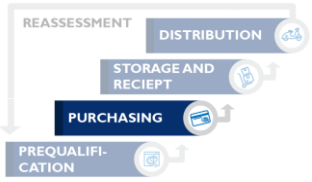
Summarize the assessment outcomes and inform the manufacturer
Prepare a list of prequalified products and manufacturers

The outcomes of the evaluation of product information package, cGMP compliance, and laboratory results for samples analyzed, if applicable, should be collated and used as the grounds for making the decision to accept or reject a product and/or manufacturer. The procurement agency should inform the manufacturer in writing of the outcome of the prequalification of each product manufactured at each specified site.

The unit or appointed person responsible for prequalification should record the outcome of the prequalification process in a list of prequalified products and manufacturers. The list should be product- and manufacturing-site specific. The list may be published in the public domain.

The procurement agency should have an agreement with the supplier to ensure compliance with the prequalification principles and that the products supplied are the same products as were prequalified (e.g., they are manufactured at the same site and the same processes are adhered to).

The list should be reviewed and updated at regular intervals. Newly prequalified manufacturers should be added to the list as they become qualified, and non-compliant manufacturers should be removed from the list as soon as they are recognized as such.



PURCHASING

Procurement should be done with the aim of purchasing effective, safe, and quality-assured products, and should not be focused on price alone. To be effective, the procurement agency should ensure that the following principles are applied in purchasing:

- Prequalified products are purchased from approved manufacturers or suppliers.
- Procurement and purchasing procedures are transparent.

- Activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts.
- Independent contract review is ensured.
- Purchasing is based on the defined procurement policy of the procurement agency.
- Purchasing and tender documents list all pharmaceutical products by their INN or national generic names.
- Suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability, and minimum order quantities.
- Intellectual property rights are respected in accordance with best practice and national law.

Purchasing should be done by personnel with appropriate qualifications and training. The personnel responsible for purchasing should be independent from those responsible for prequalification and quality assurance, and should sign confidentiality agreements and declarations of conflict of interest. The personnel should follow transparent, written procedures throughout the process of purchasing and should use explicit criteria for deciding to whom to award contracts. Procurement should be planned properly, and procurement performance should be monitored regularly.

The procurement process and products to be purchased need to comply with the destination country's legislation on registration and licensing status, quality standards, and intellectual property rights.

Whatever the procurement method, only prequalified products should be procured. Awards should be made to the manufacturer of the lowest acceptable offer for the prequalified product that meets the defined terms and conditions. The reference prices for MNCH products from key international procurers may be found in *the International Medical Products Price Guide,* available at http://mshpriceguide.org/en/home/.

Companies should be informed of the outcome. There should be an agreement with the supplier to ensure compliance with procurement principles and that products supplied are the same products as were prequalified (i.e., they are manufactured at the same site and the same processes are adhered to).

Monitor performance of manufacturers of prequalified products

There should be a procedure for continuous monitoring of the performance of manufacturers and suppliers. This may be a joint responsibility of the QA personnel and the purchasing group. If a decision is made to remove a product, manufacturer, or supplier from the list, the supplier or manufacturer should be notified and a mechanism should be in place to prevent purchasing from this supplier or manufacturer.

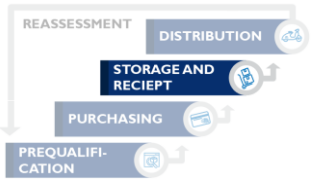
Monitoring may include:

- Review of quality control test results
- Verification that product batches supplied have been manufactured in compliance with standards and specifications accepted in the product dossier through inspection
- Pharmacovigilance (i.e., management of adverse event reporting)
- Review of rejected or failure batches

- Monitoring of complaints and recall
- Outcome of reinspection of manufacturing sites
- Outcome of reevaluation of product information
- Monitoring of direct and indirect product costs
- Monitoring of adherence to delivery schedules

Random samples of batches of pharmaceutical product(s) supplied by manufacturers of prequalified products, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g., a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring program.

The monitoring process should include continuous commercial monitoring that includes tracking of lead time and monitoring for compliance with all contract terms and conditions.



RECEIPT AND STORAGE

The procurement agency should ensure that pharmaceutical products purchased are received and stored correctly and in compliance with Good Storage Practices (GSP) and GDP, as well as applicable legislation and regulations. Receipt and storage should be done in such a way that their quality and integrity is preserved, batch traceability is maintained, and stock can be rotated.

It is recommended that premises for storage are designed in such a manner that products will follow a unidirectional flow from receiving to dispatch to avoid any possible mix-ups. Effective measures should be in place to ensure the security of products.

Quality control during receipt and storage of products is important to ensure that the quality of products is satisfactory for their intended purpose before release for use. QA comprises pre-shipment and post-shipment quality control, as detailed below. The quality control unit will be in charge of quality control testing and release of received products for distribution. The analyses may be performed by a contracted laboratory, which must comply with cGMP and GLP for control laboratories. The use of a WHO-prequalified quality control laboratory or an accredited laboratory is recommended. The quality control laboratory must be capable of undertaking the full range of tests required.

Quality assurance approaches for receipt and storage of purchased products

Pre-shipment quality control

Pre-shipment is considered at the manufacturer level prior to sending the product(s) to the procurement agency or customer.

Each batch of pharmaceutical product should be tested by the manufacturer to determine that it conforms satisfactorily to its finished product specification, prior to supply. The batch

release is evidenced by the COA, which should follow the WHO model[5] and include the results of all tests performed in comparison with the established acceptance criteria (limits), and a conclusion statement indicating the results are found to comply with product specifications.

The procurement agency may decide, using a risk-based approach, to test selected batches. It may not be necessary to do quality control testing for all products. One approach can be to limit quality control testing to those products that are not WHO-prequalified or that have no registration with an SRA. More details can be found in Module II.

Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Receipt of products

Incoming products should be cleared safely and promptly from the port of arrival. The procurement agency should ensure that all authorizations/permits or waivers necessary for the importation and customs clearance of products into the country of use are readily available prior to the delivery of the products. Specific arrangements may need to be made with local handling agents and customs to ensure speedy handling and clearance.

The person responsible for receiving the products should be independent of the person responsible for purchasing the products.

Receiving and dispatch bays should protect products from the weather. Receiving areas should be designed and equipped to allow containers of incoming products to be cleaned (de-dusting) if necessary before storage.

All incoming products should be quarantined immediately after receipt until they are released for use or distribution. Products should be quarantined until test results confirm that the products meet all of the requirements, specifications, and terms and conditions of the purchase order. Review of COAs is strongly recommended to confirm that products delivered adhere to what was ordered and are certified by the manufacturer to meet specifications.

Upon receipt, each incoming delivery should be checked for correspondence between the order, the delivery note, the supplier's labels and transport conditions (i.e., temperature and relative humidity as appropriate). The consignment should be examined for integrity of packages and seals, and uniformity of containers. Should the delivery consist of more than one batch, it should be subdivided according to supplier batch number.

Containers should be cleaned, where necessary, and labeled, if required, with the required data (i.e., label description, batch number, type, and quantity). Containers and products should be visually inspected for possible contamination, tampering and damage, expiry date, compliance with labeling and packaging instructions, and any suspect containers. If there is evidence of any irregularities, the entire delivery should be quarantined. Damage to containers and any other problem that might adversely affect the quality of the product should be recorded and investigated.

[5] World Health Organization. 2002. "Model Certificate of Analysis." Annex 10 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 36th Report. WHO Technical Report Series, No. 902. Geneva: WHO. Available at http://apps.who.int/medicinedocs/pdf/h3009e/h3009e.pdf

Segregation must be provided for the storage of rejected, recalled, or returned materials or products. Such areas, materials, and products shall be suitably marked and secured. Access to these areas and materials shall be restricted.

Post-procurement quality control

Post-procurement quality control is considered at the procurement agency level or at the level of the customer. It is part of continuous monitoring of the performance of the manufacturers and suppliers.

The procedures for receipt of products should include random sampling for independent laboratory analysis by the procurement agency to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure and with national legislation.

Products may also be randomly sampled at the end of the distribution chain and sent for independent analysis. Representative samples should be taken from containers in the consignment. Samples should be analyzed for compliance with the product specification.

Samples should be taken only by appropriately trained and qualified personnel and strictly in accordance with written sampling plans and sampling instructions based on a risk assessment.[6],[7],[8] Containers from which samples have been taken should be labeled accordingly.

Stringent precautions should be taken to ensure that rejected products cannot be used. This can be achieved through separate storage or by means of a validated computerized system. Rejected products may await destruction or be returned to the supplier. They should be handled in accordance with a written procedure. Whatever action is taken should be approved by authorized personnel and recorded.

Storage of products

All staff should be trained to observe high levels of personal hygiene and sanitation. Personnel employed in storage areas should wear protective or working garments appropriate for the activities performed.

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of products, including space for segregation of rejected, expired, recalled or returned stock. Adequate ventilation should be in place to control temperature and relative humidity.

Highly hazardous, poisonous, and explosive materials such as narcotics, psychotropic drugs, and substances presenting potential risks of abuse, fire, or explosion must be stored in safe and secure areas. Adequate fire protection measures must be ensured in conformity with the rules of the concerned civic authority.

All products should be stored in an orderly fashion to permit batch segregation and stock rotation according to the first-to-expire-first-out rule. Stock should be stored off the floor

---

[6] International Organization for Standardization (ISO). 1999. Sampling Procedures for Inspection by Attributes: Sampling Schemes Indexed by Acceptance Quality Limit for Lot-by-Lot Inspection. British Standard BS 6001-1:1999/International Organization for Standardization, ISO 2859-1:1999. Geneva: ISO.

[7] American National Standards Institute (ANSI). n.d. Sampling Procedures and Tables for Inspection by Attributes. ANSI/ASQCZ1.4 and ANSI/ASQCZ1.9. Washington, DC: ANSI.

[8] World Health Organization. 2005. "WHO Guidelines for Sampling of Pharmaceutical Products and Related Materials." Annex 4 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 39th Report. Technical Report Series, No. 929. Geneva: WHO. Available at http://apps.who.int/medicinedocs/documents/s21440en/s21440en.pdf

and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair, and contents on pallets should be stacked in a manner that ensures there is no damage to containers on the lower level.

All products should be stored under the appropriate conditions as established by the manufacturer, which are based on the results of stability testing. Where special storage conditions are required (i.e., for temperature and humidity), these should be provided, checked, and monitored, and records maintained.

Temperature mapping of the facility should be well designed to support assurance of uniformity of the temperature across the storage facility. It is recommended that temperature monitors and relative humidity monitors (if required) be placed in the worst-case areas of the facility. Recorded monitoring data should be available for review.

Equipment used for continuous monitoring should be calibrated at suitable, predetermined intervals and results should be recorded, reviewed, and retained. Out-of-limit and out-of-trend results should be investigated in accordance with an SOP and appropriate action should be taken. All monitoring records should be kept for at least one year after the end of the shelf-life of the stored product, or as long as required by national legislation.

Cold rooms should be provided for storage of products requiring storage between 2°C and 8°C—for example, for oxytocin injection. Cold rooms should be qualified, which includes temperature mapping. The temperature should be controlled, monitored, and recorded, with results reviewed for compliance with the specified limits. Where electronic systems are used for data collection, provision should be made for backup of data at regular and defined intervals. Cold rooms should be fitted with alarm systems that will alert personnel to out-of-limit conditions.

Note: The use of the vaccine cold chain to store other products requiring storage between 2°C and 8°C may make it unnecessary to invest in maintaining multiple cold chain infrastructures.

Stock rotation and control is best maintained by the use of a validated stock control system. Care must be taken to select a system that can manage the rigid requirements for batch number control and expiry date, which are essential for handling pharmaceutical products.

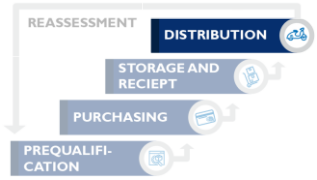
Periodic stock reconciliation should be performed, comparing actual and recorded stock levels. All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix-ups and/or incorrect issue. Records should be maintained.

Damaged containers should not be issued unless it is certain that the quality of the product inside is unaffected. Any damaged containers should be reported without delay to the person responsible for quality assurance. Any action taken should be in accordance with a written procedure and documented.

All stock should be checked regularly for obsolete and outdated products. All due precautions should be observed to prevent issue of outdated products. The handling of such materials should be subject to a written procedure.

Recalled products should be identified, recorded, reconciled, and stored separately in a secure area until a decision has been made regarding their disposition. The decision should be made as soon as possible, in coordination with the manufacturer. An assessment should be made by an appropriately qualified and experienced member of staff.

Returned goods should be handled in accordance with a written procedure. They should be placed in quarantine until a decision has been made regarding their disposition. Products returned from the customer should be destroyed in compliance with national requirements unless it is certain their quality is satisfactory. In that case, they may be considered for resale. The nature of the product, any special storage requirements, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. If any doubt arises over the quality of the product, it should not be considered suitable for reissue. Any action taken should be recorded.



DISTRIBUTION

The procurement agency should have a well-managed distribution system that achieves these objectives:

- Maintain a constant supply of medicines
- Keep medicines in good condition throughout the distribution process
- Ensure controlled transport conditions
- Minimize losses of medicines due to spoilage and expiry
- Maintain accurate inventory records
- Rationalize medicine storage points
- Use available transportation resources as efficiently as possible
- Reduce theft and fraud
- Provide information for forecasting medicine needs

Measures to ensure product integrity and quality during distribution

To ensure product integrity and quality during distribution, the principles established in the WHO *Guidelines for Good Trade and Distribution Practices for Pharmaceutical Starting Materials*[9] should be followed.

Transport condition

Pharmaceutical products should be transported in such a way that the integrity of the product is not adversely affected and appropriate storage conditions are maintained. Where temperature excursions occur during transport, risk assessment should be done to ensure that an informed decision is made as to the fate of the products.

Every precaution should be taken to minimize the risk of theft and fraud. Different measures and strategies could be considered for preventing theft and fraud, including but not limited to: inventory control; using locked containers; shrink-wrapping entire pallets in plastic; using

[9] World Health Organization. 2004. "Good Trade and Distribution Practices for Pharmaceutical Starting Materials." Annex 2 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 38th Report. WHO Technical Report Series, No. 917. Geneva: WHO. Available at http://apps.who.int/medicinedocs/pdf/s4899e/s4899e.pdf

unique identifiers (e.g., use uniquely identifiable and difficult-to-defeat tamper-indicating devices, imprint all containers and external packing with a unique seal or monogram, register batch numbers on all immediate containers and external packing and agree not to sell products from the same batch to any other buyer, use electronic tagging devices); imprinting containers and packaging; and batch number registration.

Cold chain

Special care should be exercised when using a cold chain. If pharmaceutical products are distributed under controlled cool or cold conditions, appropriate containers should be used. Containers should be packed following established SOPs to ensure that products are not negatively affected.

When a cooling agent, such as dry ice, is used in a cold chain, it is necessary to ensure that the product does not come in contact with the cooling agent as this may adversely affect the quality of the product, (e.g., as a result of freezing).

The process should be validated to cover the expected transport time, taking into account expected environmental conditions.

Temperature and relative humidity monitoring and records

Calibrated devices should be used to monitor conditions such as temperature and relative humidity (when it is required) during transportation. Records should be available for review.

Dispatch of products

Rules for dispatch procedures should be established according to the nature of the pharmaceutical products being dispatched and after taking into account any special precautions observed. Any special packaging requirements for movement of products must be met. Some products may require special protection before they can be shipped by sea or by air. All legislation that may affect these requirements must be complied with.

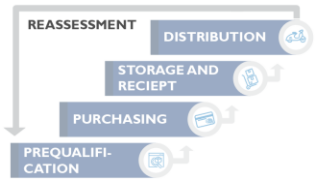
The outside container should offer adequate protection from all external influences and should be indelibly and clearly labeled. Products should be packed in such a way as to minimize the risk of theft (e.g., by using locked containers or by shrink-wrapping entire pallets in plastic).

Records for dispatch should be retained, stating at least the following: date of dispatch; customer's name and address; product description (e.g., name, dosage form and strength [if appropriate], batch number and quantity); and transport and storage conditions.

Traceability

Distribution records should contain sufficient information to enable traceability of the product from the point of supply to the point of delivery. Traceability of products is crucial in case of the need for product recalls. It will also help to detect theft and fraud. Any discrepancies should be investigated and followed up by appropriate measures to tackle possible security breaches.

In addition to the distribution records, several technologies are available for the tracking of products from production to consumer; for example, the printing of 2D codes (like Datamatrix) on packages, the use of forensic inks packs, cryptographic signature, security seals, radiofrequency ID (RFID) labels, packaging with special materials, laser surface, or the combination of multiple technologies. These technologies allow more stringent control of the supply chain; however, their use could increase product cost.



REASSESSMENT

The quality of all products procured should be continuously monitored. Requalification or reevaluation should occur at regular intervals to ensure that products procured continue to meet defined norms and standards.

Principles of routine and non-routine reevaluation of products and manufacturers

Reevaluation of products

Product information should be reviewed every five years or sooner if major changes occur in the meantime. The procurement agency should have a mechanism in place to ensure that manufacturers inform them of any contemplated changes to the product that may affect its safety, efficacy, or quality. With regard to the product, manufacturers should report the following:

- Change of manufacturing process, site or equipment relating to the product
- Change of contract manufacturers
- Change of pharmaceutical product release control laboratories
- Change of manufacturers of API or container or closure
- Changes to the formulation or composition of the product
- New analytical method in the testing of API, intermediate or finished product
- Change of specifications
- Change in shelf life

Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data, and should inform the purchasing group about the changes and the result of the evaluation of such changes.

Non-routine reevaluation of products should be done in the following cases:

- If there is any omission by the manufacturer in the initial evaluation procedure, or evidence of omission during follow-up activities in relation to the requirements, including compliance with quality system standards and failure-to-notify complaints
- If any batch or batches of supplied product(s) are documented by the procurement agency as not being in compliance with the agreed specifications of the product or as revealing failure(s) regarding safety, performance or quality of the product
- If the investigation of a complaint leads to the conclusion that the quality and/or safety of the product is in question

- If any fraud or misconduct by the manufacturer is evident
- If any batch or batches of product(s) was supplied and is considered not to be in compliance with the agreed specification of the product
- If a complaint considered to be serious in nature has been received by the organization
- If, in the opinion of the organization, changes made in the sourcing of the API, formulation, manufacturing method, facility or other production aspects require a reassessment be made
- If supply has been suspended for one year or longer

In cases of changes or variations to products, the *WHO publication Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for Medicines Regulatory Authorities[10] (13)* provides guidance on when to proceed with which type of reevaluation

The procurement agency should suspend or withdraw a prequalified product and its manufacturing facility from the requalification list if there is evidence of non-compliance with the requirements for prequalification.

Reevaluation of manufacturers

Reinspection of manufacturers should take place at regular intervals based on a risk assessment, but no less often than every five years. Procurement agencies should have a mechanism in place that ensures that manufacturers inform them immediately of any changes to the manufacturing site, manufacturing process, or equipment that may have an impact on its prequalification. Non-routine requalification may be required in the following situations:

- If any information was omitted in the initial assessment
- If false or misleading information is suspected during the follow-up assessment
- If changes are implemented that may impact the prequalification of the manufacturing site, such as changes to key personnel or organizational structure, changes to equipment, apparatus or the manufacturing process, or the renovation or addition of facilities requiring validation, commissioning, or reinspection
- If a complaint considered to be serious in nature has been received

The procurement agency should suspend or withdraw a prequalified product and its manufacturing facility from the requalification list if there is evidence of non-compliance with the requirements for prequalification.

Monitoring of product quality and complaints

Random samples of batches of prequalified pharmaceutical product(s), taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g., a WHO-prequalified

[10] World Health Organization. 2011. Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for National Medicines Regulatory Authorities (NMRAs). 2nd ed. Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf;jsessionid=49861414B7761E8954861D6069D3A9DB?sequence=1

laboratory) for compliance with final product specifications as part of the continuous monitoring program.

Complaints should be handled in accordance with a written procedure. Any complaint concerning a pharmaceutical product or batch of products supplied should be thoroughly investigated and include a root cause analysis, risk assessment, and effective CAPA to avoid recurrence.

A written report of the complaint, investigation, effective implementation of the CAPA, and outcome should be available. The nature of the complaint should be communicated to the manufacturer. The outcome of the investigation should be communicated to the complainant.

MODULE II

PRAGMATIC APPROACH TO ASSURE QUALITY OF MNCH PRODUCTS

MODULE II

PRAGMATIC APPROACH TO ASSURE QUALITY OF MNCH PRODUCTS

Pharmaceutical products that have achieved SRA approval, have been prequalified by the WHO PQTm, or have a positive ERP recommendation are considered high-quality and therefore widely recommended for procurement. However, many MNCH products are not covered by the WHO PQTm, ERP, or an SRA. Moreover, procurement agencies have limited capacity and often are not able to assess the product information package and manufacturing site in the way that those stringent bodies do. A pragmatic approach is therefore necessary for procurement agencies with limited capacity, in order to support their procurement QA system and allow timely access to additional quality MNCH products beyond the WHO PQTm, SRA, or ERP coverage, to serve patient needs.

All pharmaceutical products must be approved by the NMRA in the country where they will be used. And, in addition, products should be only be procured if the product meets the following criteria:

1. The products are WHO prequalified by the WHO PQTm OR are approved by a stringent regulatory authority (soon to be replaced by WHO Listed-authorities).

   OR

2. In the absence of either WHO-prequalified or SRA-approved, on an interim basis, they are approved by a qualified Expert Review Panel, convened by WHO

   OR

3. In the absence of WHO-prequalified or SRA-approved or qualified by an ERP, products should be procured through accredited sources such as wholesalers which are recognized/accredited (i.e., GDP, ISO certified) by established entities as meeting a minimum level of product testing by a WHO PQP Control Laboratory, which

would determine whether the product is substandard or falsified.
As with ERP, this does not ensure the products's quality, but provides a high level of confidence that the product is not substandard or falsified.
When it is necessary to adopt this process, such procurement approvals should be limited to 12 months.

Quality assurance of these products requires several components:

- Accordance with international standards of manufacturing quality (i.e., ICH or WHO), assessed independently by qualified experts
- Assured compliance with international cGMP (i.e., ICH or WHO) after site inspection by independent experts
- Assessment by an organization that can impose significant consequences for non-compliance

This module describes different assessment processes, documentation requirements, and quality control requirements, based on the registration status of the product to be prequalified, that should be considered to assure the quality of MNCH products during the prequalification and procurement.

ASSESSMENT PROCESS

There are two possible assessment approaches, abridged assessment or full assessment, as discussed below.

Abridged Assessment

Abridged assessment can be done for products already prequalified by the WHO PQTm, approved by an SRA, positively assessed by ERP, or registered by the NMRA of the country of use or other recognized NMRAs. The procurement agency can recognize the scientific evaluation of pharmaceutical products that has been conducted by those parties to facilitate and accelerate the prequalification process, and optimize use of procurement agency's and manufacturers' resources.

Under the abridged assessment procedure, the manufacturer shares evidence of previous regulatory approval with the procurement agency such as the WHO prequalification approval letter, marketing authorization or CPP issued by the SRA or recognized NMRA, the ERP letter indicating recommendation for use, and other documents as indicated in this module's Section 2, Documentation Requirements. The procurement agency then bases its decision to prequalify the product on the basis of this information to avoid repeating the comprehensive assessment.

Note: The validity period of the ERP recommendation is usually limited to a maximum duration of 12–18 months from the time of the ERP recommendation, depending on the quality assurance policy of the procurement agency that commissioned the ERP review. Therefore, the procurement agency that wishes to adopt the ERP recommendation needs to verify its validity at that point in time and undertake a risk analysis for the limited-time procurement.

Full Assessment

When the procurement agency needs to procure a product that has no WHO prequalification, regulatory approval from the SRA or other recognized NMRAs or ERP recommendation, a full assessment of the documents demonstrating quality, safety, and efficacy of the product, as indicated under Section 2(c) below, should be carried out. The procurement agency, through its technical experts or appointed qualified external evaluators, has to assess the quality risks of the product to make a decision regarding time-limited procurement, during which time the manufacturer is expected to progress along the NMRA registration process or waiving the registration requirement.

Risk assessment is applied to the following major product attributes for the submitted product:

- GMP status of the manufacturing site
- FPP manufacture and controls
- Stability and shelf life
- API sources and quality
- Evidence of therapeutic equivalence

The following deficiencies should be considered as "objection to procurement":

- Evidence of GMP compliance is insufficient.
- FPP specification or analytical validation for a critical test parameter are unacceptable; for sterile products, the manufacturing process is not adequately validated.
- The available stability data do not allow any assignment of product shelf life.
- Efficacy and safety data have not submitted, or are unsatisfactory (e.g., several major deficiencies).
- API specification is not acceptable for a critical test parameter such as impurities.

For the product that has deficiencies listed below, procurement may be considered only when there are no alternatives, and provided the benefit outweighs the risk of procuring a product that lacks full quality assurance. These deficiences include:

- The FPP specification is acceptable but analytical methods are not sufficiently validated.
- Shelf life is supported by insufficient stability data (e.g., submission of data on only one batch of a product with potential stability problems).
- Bioequivalence data have not been submitted, but for orally administered products, multimedia dissolution data show similarity (i.e., for non-oral products other in vitro data, as applicable, indicate similarity), AND/OR the comparator is a generic product not prequalified or SRA-authorized.
- The API has acceptable specifications but GMP issues have been identified.

Samples should be analyzed for a product that does not possess regulatory approval from the NMRA of country of use or other recognized NMRAs or when the quality is in doubt, to ensure compliance with the finished product specification. The procurement agency should ensure that the testing laboratory complies with cGMP and GLP. The use of a WHO-

prequalified quality control laboratory or an ISO:IEC 17025 accredited laboratory is, therefore, recommended.

DOCUMENTATION REQUIREMENTS

The type of product information package required for submission during the prequalification process will depend on the registration status of products to be prequalified, as reviewed below.

A. Products prequalified by the WHO PQTm, approved by an SRA, or positively assessed by the ERP

The products already prequalified by the WHO PQTm, approved by an SRA, or positively assessed by the ERP are considered quality-assured and therefore recommended for prequalification and procurement.

The procurement agency should stipulate that the submitted product be the same as the products approved under WHO PQTm or SRA or ERP in terms of all the technical characteristics, including:

- Same composition for both API and excipients
- Same API and excipient sources
- Same manufacturing facility/line/equipment/building
- Same specifications for the API
- Same specifications for the FPP
- Same type of packaging material

Any differences should be declared and justified by the manufacturers as not having any impact on altering the safety, efficacy, and quality of the FPP.

Abridged assessment can be carried out since the product has already passed the stringent evaluation of quality, safety, and efficacy. The following information/documents should be included in the product information package to be submitted to the procurement agency for abridged assessment during the prequalification process:

- A statement confirming that the FPP, including but not limited to composition/formulation, strength, manufacturing process, specifications, packaging, and product information, will, at the time of submission and after prequalification, in all respects be the same as the product prequalified by WHO PQTm, registered with the reference SRA, or recommended for use by the ERP
- A copy of the WHO prequalification approval letter, marketing authorization issued by the reference SRA, or the ERP letter indicating recommendation for procurement, or the equivalent thereof, to demonstrate that the product is already prequalified by the WHO PQTm, approved by SRAs, or reviewed and recommended for use by the ERP
- The approved product information (i.e., Summary of Product Characteristics or an equivalent thereof; the patient information leaflet or equivalent thereof; and the labeling)

- Samples of the same product for which prequalification is requested, to enable visual examination with respective COA

The product must be authorized by the NMRA in the country of use before it can be procured and supplied to the country. The procurement agency should work closely with the NMRA to ensure that expedited registration process is applied to accelerate an access to the product. The NMRA is encouraged to recognize the WHO prequalification approval letter, marketing authorization issued by the reference SRA, and the ERP letter indicating recommendation for procurement, to avoid duplication of assessment

B. Products approved by the NMRA in the country of use or other recognized NMRAs:

The NMRA is responsible for the quality assurance of medicines, including evaluation of the quality, safety, and efficacy data of the finished pharmaceutical products and inspection of the corresponding manufacturing facilities according to current international norms and standards. However, some NMRAs may not maintain their regulatory requirements or evaluation systems in line with the current international norms and standards. Therefore, the procurement agency should consult with the NMRA and WHO to determine whose regulatory approval can be recognized and an abridged assessment can be carried out.

The procurement agency should require that the submitted product be the same as the products approved by the NMRA, in the country of use or other recognized NMRAs, in terms of all the technical characteristics including:

- Same composition for both API and excipients
- Same API and excipient sources
- Same manufacturing facility/line/equipment/building
- Same specifications for the API
- Same specifications for the FPP
- Same type of packaging material

Any differences should be declared and justified by the manufacturers as not having any impact on the safety, efficacy and quality of the FPP.

Abridged assessment can be carried out since the product has already passed the evaluation of quality, safety, and efficacy according to international norms and standards. The following information/documents should be included in the product information package submitted to the procurement agency for abridged assessment during the prequalification process:

- A statement confirming that the FPP, including but not limited to composition/formulation, strength, manufacturing process, specifications, packaging, and product information, will, at the time of submission and after prequalification, in all respects be the same as the product approved by the NMRA in the country of use or other recognized NMRAs
- A copy of the marketing authorization or current CPP issued by the NMRA in the country of use
- Evidence of GMP compliance such as GMP certificate, inspection report issued by the recognized NMRA, or regional registration harmonization initiatives

- The approved product information (e.g., SmPC or an equivalent thereof, PIL or equivalent thereof, and the labeling)
- Samples of the same product for which prequalification is requested, to enable visual examination with respective COA

C. When the conditions established in A. and B. are not met, or there is a need to reassess the product quality

When the registered products may not meet the previous criteria set by the procurement agency or when there are not enough registered products available, the procurement agency may need to obtain the products from unregistered sources. The procurement agency should request the manufacturers to:

- Register the products with the NMRA in the country of intended use

OR

- Apply for a waiver, if they are able to meet the conditions for waiving the registration requirements as indicated by the NMRA in the country of intended use

The procurement agency should work closely with the NMRA to ensure that mechanisms or regulations are in place to fast-track registration or to waive the registration requirements, in order to facilitate government tenders.

To assure the quality of the product, full assessment should be carried out. The manufacturers should be requested to provide the following information/documents in the product information package for the procurement agency to review during the prequalification process:

- A copy of the marketing authorization, current CPP, or manufacturing authorization (certifying that the firm is allowed to manufacture the submitted product) issued by the NMRA in the country of origin
- Registration status in other countries, including all information on where the product has been withdrawn from the market, or on where application has been rejected, deferred or withdrawn
- Evidence of GMP compliance such as GMP certificate, inspection report issued by the competent NMRA
- Product quality review
- FPP manufacturing process
- API and FPP specifications in compliance with recognized standards from internationally recognized pharmacopoeia (e.g. United States, British, European or International Pharmacopoeias)
- Stability testing data (both accelerated and real time studies) as per ICH and/or WHO guidelines
- Evidence of safety and efficacy (e.g., bioequivalence data, data to support bio-waiver)
- The approved product information (e.g., Summary of Product Characteristics or an equivalent thereof, product information leaflet or equivalent thereof, and the labeling).

- Samples of the product with sufficient number of dosage form units to perform full laboratory analysis, including the respective COA

Technical experts of the procurement agency should review and perform a risk assessment of the information obtained to reach a conclusion as to the potential acceptability of the limited-time procurement. This assessment mechanism is a temporary solution to pursue while the product undergoes registration or a waiver for registration requirement is in process with the NMRA.

Suitably qualified external evaluators may be appointed, subject to compliance with the policy of the procurement agency regarding aspects such as confidentiality, conflicts of interest, and financial resources.

QUALITY CONTROL REQUIREMENTS

Quality controls consist of pre-shipment quality control at manufacturer level prior to sending the product to the procurement agency, post-shipment quality control at the procurement agency level, and postmarketing surveillance to ensure that the products are properly stored and always meet the desired quality for use by the patient. The quality control requirements will depend on the registration status of products to be prequalified, as reviewed below.

A. Products prequalified by the WHO PQTm, approved by an SRA, or positively assessed by the ERP

Pre-shipment quality control:

- Pre-shipment quality control is required at manufacturer level prior to sending the product to the procurement agency.
- The procurement agency should check the COA issued by the manufacturer to confirm that the product delivered is the same that was prequalified and ordered and is certified to meet FPP specification.

Post-shipment quality control including import control (inspection and quality control testing on importation and arrival at the distribution/storage warehouse):

- Post-shipment quality control may be considered at the procurement agency level.
- Products may be randomly sampled and sent for independent laboratory analysis. Testing should be done to assess compliance with the product specifications. Use of a laboratory compliant with international standards (e.g., WHO-prequalified or ISO:IEC 17025 accredited) is recommended to ensure the accuracy of results.

Post-marketing surveillance:

- The products should be regularly sampled and tested as part of a risk-based post-marketing strategy to ensure that products are properly stored and always meet the desired quality for use by the patient. This will also help to identify substandard and falsified medicines that may have been smuggled into the supply chain.

B. Products approved by the NMRA in the country of use or other recognized NMRAs

Pre-shipment quality control:

- Pre-shipment quality control is required at the manufacturer level prior to sending the product to the procurement agency.
- The procurement agency should conduct pre-shipment inspections on randomly selected shipments through an independent inspection agent. The independent inspection agency is in charge of collecting the samples and forwarding them to a laboratory compliant with international standards (e.g., WHO-prequalified or ISO:IEC 17025 accredited) for quality control testing. This process is in addition to the manufacturer's own quality control testing.

Post-shipment quality control including import control (inspection and quality control testing on importation and arrival at the distribution/storage warehouse):

- Post-shipment quality control may be considered at the procurement agency level.
- Products may be randomly sampled and sent for independent laboratory analysis. Testing should be done to assess compliance with the product specifications. Use of a laboratory compliant with international standards (e.g., WHO-prequalified or ISO:IEC 17025 accredited) is recommended to ensure the accuracy of the results.

Post-marketing surveillance:

- The products should be regularly sampled and tested as part of a risk-based post-marketing strategy to ensure that the products are properly stored and always meet the desired quality for use by the patient. This will also help to identify substandard and falsified medicines that may have been smuggled into the supply chain.

C. When the conditions established in A. and B. are not met, or there is a need to reassess the product quality

Pre-shipment quality control:

- Pre-shipment quality control is required at the manufacturer level prior the product is forwarded to the procurement agency.
- The procurement agency should conduct pre-shipment inspections on each shipment through an independent inspection agent. The independent inspection agency is in charge of collecting the samples that are sent to a WHO-prequalified or ISO:IEC 17025 accredited quality control laboratory for testing. This process is in additional to the manufacturer's own quality control testing.

Post-shipment quality control including import control (inspection and quality control testing on importation and arrival at the distribution/storage warehouse):

- Post-shipment quality control is required at the procurement agency level.
- Products should be randomly sampled and sent for independent laboratory analysis. Use of a WHO-prequalified or a ISO:IEC 17025 accredited quality

control laboratory is required to ensure the accuracy of the results. The samples should be analyzed for compliance with the product specifications.

Post-marketing surveillance:

- The products should be regularly sampled and tested as part of a risk-based post-marketing strategy to ensure that the products are properly stored and always meet the desired quality for use by the patient. This will also help to identify substandard and falsified medicines that may have been smuggled into the supply chain.

MODULE III

TECHNICAL INFORMATION FOR LIFE-SAVING MNCH PRODUCTS

OXYTOCIN

MISOPROSTOL

HEAT-STABLE CARBETOCIN

MAGNESIUM SULFATE

HYDRALAZINE

METHYLDOPA

TRANEXAMIC ACID

GENTAMICIN

7.1% CHLORHEXIDINE DIGLUCONATE

AMOXICILLIN

ORAL REHYDRATION

ZINC

MODULE III

TECHNICAL INFORMATION FOR LIFESAVING MNCH PRODUCTS

This module provides useful technical information of life-saving MNCH products to assist the national government procurement agencies in establishing technical specifications for the product(s) to be prequalified and/or evaluating the product information package submitted by the manufacturer when the full assessment is necessary. The information provided in this module is based on the review of compendial monographs and literature, and on internal expert consultations.

The following MNCH products are included in this module are as follows:

MATERNAL HEALTH	**Oxytocin** injection 10 IU mL	Post-partum haemorrhage
	Misoprostol tablets, 200 micrograms	Post-partum haemorrhage
	Heat-stable Carbetocin injection, 100 micorgrams/mL	Post-partum haemorrhage
	Tranexamic Acid injection, 100 mg/ 10 mL ampoule	Post-partum haemorrhage
	Magnesium sulfate injection 500 mg/mL in 2-mL and 10-mL ampoule	Eclampsia and severe pre-eclampsia
	Hydralazine powder for injection, 20 mg in 2-mL ampoule	Acute management of severe pregnancy-induced hypertension
	Methyldopa tablets, 250 mg	Acute management of severe pregnancy-induced hypertension
NEWBORN	**Gentamicin injection**	Newborn sepsis
	7.1% Chlorhexidine Digluconate solution or gel for umbilical cord care	Newborn cord care

CHILD HEALTH	**Amoxicillin** dispersible tablets, 250 mg	Pneumonia
	Oral rehydration salts (ORS)	Diarrhea
	Zinc sulfate, gluconate, acetate and citrate; dispersible tablets 10 mg, 20 mg; oral solution 10 mg per unit dosage	Diarrhea

OXYTOCIN

INJECTION 10 IU IN 1-ML

GENERAL PRODUCT INFORMATION

Postpartum hemorrhage (PPH) refers to excessive bleeding after childbirth. Left untreated, it can lead to anemia, shock, and also death. PPH is the leading cause of maternal death in low- and middle-income countries. Proper screening, prevention, and treatment of PPH can save women's lives and reduce global burden of maternal mortality.

Prevention and treatment for most cases of PPH require the use of a uterotonic medicine to increase muscle contractions in the uterus that compress the blood vessels. In settings where multiple uterotonic options are available, WHO recommends oxytocin as the uterotonic agent for the prevention and treatment of PPH for all births. In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other uterotonics injectable ergometrine or oral misoprostol is recommended for the prevention and treatment of PPH. It is also prioritized as an essential medicine by the UN Commission on Life-Saving Commodities for Women and Children.

Other uterotonic medicines, such as misoprostol, carbetocin, ergotamine and ergometrine, have some drawbacks. Misoprostol is recommended by WHO for the prevention and treatment of PPH where oxytocin is unavailable (or its quality cannot be guaranteed). It is recommended for use in women giving birth outside of a health facility for PPH prevention (e.g., home deliveries), as it is administered as a pill rather than by injection. Carbetocin has a heat-stable formulation that does not require cold-chain storage and transportation and it is recommended by the WHO for the prevention of PPH in settings and contexts where its cost is comparable to other effective uterotonics.[1] Unlike oxytocin, carbetocin is not indicated for treatment of PPH and is contraindicated for induction or augmentation of labor. Ergotamine and ergometrine have more side effects, should only be given after the birth of the placenta, must be kept in the cold chain

[1] WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1

and out of light and are contraindicated for many conditions, including hypertension and pre-eclampsia.

Oxytocin is the safest and most effective uterotonic medicine for the prevention and treatment of PPH, which should be procured over other uterotonic medicines and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

According to the WHO recommendations on routes of oxytocin administration for the prevention of PPH,[2] the use of oxytocin (10 IU, intramuscular/intravenous) is recommended for all births. In situations where women giving birth vaginally already have intravenous access, the slow intravenous administration of 10 IU oxytocin is recommended in preference to intramuscular administration.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

2. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use as oxytocin is an injectable medicine.

3. As per the WHO/UNICEF/UNFPA joint statement, procurers and distributors of oxytocin should ensure that specifications clearly reference appropriate quality standards and requirements, including appropriate labeling for storage at 2–8°C (35–46°F), and supply chains managers should ensure that oxytocin is maintained at 2–8°C (35–46°F).

KEY QUALITY CONSIDERATIONS

Product specification

Oxytocin injection products must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

The container-closure system (ampoule/vial) must be sufficient to preserve sterility during the shelf life of the product. Additional information about oxytocin injection packaging and labeling can be found in the Annex.

[2] WHO. 2020. "WHO recommendation on routes of oxytocin administration for the prevention of postpartum hemorrhage after vaginal birth." Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/336308/9789240013926-eng.pdf

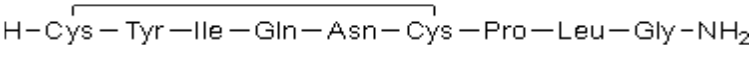
Storage, transportation, and distribution

Oxytocin that is procured should be labeled and stored between 2˚C and 8˚C from the point of manufacture to the point of use to maintain the product quality.

Although some manufacturers state the product can be stored at controlled room temperature, between 20˚C and 25˚C, it should be noted that room temperatures in health facilities in tropical countries often exceed the controlled room temperature, which can put oxytocin quality at risk.

Oxytocin is temperature-sensitive and loses effectiveness after three months of storage at temperatures above 30˚C. Significant quality issues can stem from inappropriate transport and storage, which may expose the product to high temperatures that can degrade it and result in low potency.

Detailed records of all stages of transport from the date the oxytocin product leaves the FPP manufacturer to its arrival at the procurer facility should be provided to assure the product has not been subject to adverse temperatures for a potentially harmful length of time. The procurer should reach agreement with the FPP manufacturer and/or distributor to use the most suitable transport and handling to protect the product from exposure to high temperatures. Data loggers or suitable temperature-time integrators can be used to alert procurers of any excursions during transportation and be alert to possible degradation of oxytocin.

Name of the Medicinal Product	Oxytocin injection
Chemical Name	Oxytocin (L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide) Oxytocin is a synthetic cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. Being wholly synthetic, it does not contain vasopressin and has a constant and reliable effect.
Chemical Structure	$C_{43}H_{66}N_{12}O_{12}S_2$ 

Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Oxytocin injection is a sterile solution of oxytocin or a sterile dilution of oxytocin concentrated solution in water for injection. It contains 10 IU of oxytocin per mL. List of typical excipients[3]: – Acetic acid – Chlorobutanol – Ethanol – Sodium acetate trihydrate – Water for injection
Packaging and Presentation	The WHO Essential Medicines List states "oxytocin injection 10 IU in 1-mL," which does not preclude procurement of any particular presentation of injectable oxytocin. Oxytocin injection is generally packed in glass ampoules. However, some manufacturers provide the product in glass or plastic vial.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of June 2022, four oxytocin injections are prequalified by the WHO PQP, as shown below. It is recommended to check the updated information at the time of procurement, by going to https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

[3] Based on the formulation of an innovator product, Syntocinon®.

Table O-1. List of WHO Prequalified Oxytocin Injection.

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH050	PT Sanbe Farma, Jl. Taman Sari no. 10, Bandung, 40116, Indonesia	FPP manuf. site: PT Sanbe Farma, Sterile Preparation Plant, Unit 3, Jl. Industri Cimarene No. 8, Desa Cimareme, Kecamatan Ngamprah, Kabupaten Bandung Barat, 40553, Indonesia API manuf. site: Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia	Solution for injection 10 IU/mL	Ampoule; Type I glass 1 mL x 10's	30-Jun-17	18 months	Store in refrigerator (2–8˚C), do not freeze, protect from light.
RH079	JSC Grindeks, 53 Krustpils Street, Riga, LV-1057, Latvia	FPP manuf. site: - HBM Pharma s.r.o., Sklabinska 30, Martin, 036 80, Slovakia - UAB Santonika, Veiveriu str. 134B, Kaunas, LT- 46353, Lithuania API manuf. site: JSC Grindeks, 53 Krustpils Street, Riga, LV-1057, Latvia	Solution for injection 10 IU/mL	Ampoule, Type I glass 1 mL x 5's 1 mL x 10's 1 mL x 100's	14-Oct-19	36 months	Store in a refrigerator (2°C to 8°C), do not freeze.
RH083	Steril-Gene Life Sciences (P) Ltd, No.15, Gopalakrishna Road, T. Nagar, Chennai, 600 017, India	FPP manuf. site: Steril-Gene Life Sciences (P) Ltd., 45, Mangalam Main Road, Mangalam Village, Villianur Commune, Puducherry, 605 110, India API manuf. site: Hemmo Pharmaceuticals Pvt. Ltd, C-43, MIDC, Off Thane Belapur Road, TTC Industrial Area, Turbhe, Dist: Thane, 400 613, India	Solution for injection 10 IU/mL	Ampoule, USP Type I glass 1 mL x 5's 1 mL x 10's 1 mL x 100's	14-Oct-19	24 months	Store in a refrigerator (2°C to 8°C), do not freeze, protect from light.
RH097(a)	Panpharma Laboratories, ZI du Clairay, Luitre, 35133, France	FPP manuf. site: - PANPHARMA GmbH, Bunsenstrasse 4, Trittau, D-22946, Germany - Haupt Pharma Livron SAS, 1 rue Comte de Sinard, Livron sur Drôme, 26250, France API manuf. site: JSC Grindeks, 53 Krustpils Street, Riga, LV-1057, Latvia	Concentrate for solution for infusion 10 IU/mL	Ampoule, Type I glass 1mL ampoule x 10's	1-Jul-2021	36 months	Store in a refrigerator (2°C to 8°C), protect from light.

(a) Indicates SRA-approved product that has been prequalified based on abbreviated assessment.

SRA-approved products

Table O-2. Examples of SRA-Approved Oxytocin Injection 10 IU/mL in 1-mL

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Syntocinon® 10 IU/mL concentrate for solution for infusion	UK MHRA	Mylan Products Ltd, UK	PL 46302/0063	Clear glass 1-mL ampoule	5 years	Store between 2°C and 8°C. May be stored up to 30˚C for 3 months, but must then be discarded.
Oxytocin 10 IU/mL concentrate for solution for infusion	UK MHRA	Hameln Pharmaceuticals Ltd, UK	PL 01502/0097, PL 01502/0102	Clear glass 1-mL ampoule	5 years	Store between 2°C and 8°C.
Oxytocin 10 IU/mL concentrate for solution for infusion	UK MHRA	Wockhardt UK Ltd, UK	PL 29831/0625	Clear, type I, neutral glass, 1-mL ampoule	3 years	Store between 2°C and 8°C. May be stored up to 30˚C for 3 months, but must then be discarded. Store in the original package in order to protect from light.
Oxytocin 10 IU solution for injection	UK MHRA	EVER Neuro Pharma GmbH, Austria	PL 40369/0006	Colorless glass (type I) 1-mL ampoule	3 years	Store in refrigerator (2–8˚C). May be stored below 25˚C for 6 months, but then ~~must~~ discarded.
Oxytocin 10 IU/mL solution for infusion	UK MHRA	Intrapharm Laboratories Ltd, UK	PL 17509/0089	Transparent 1 ml Ph.Eur. type 1 glass ampoules	4 years	Store in a refrigerator (2–8°C). May be stored up to 30°C for 3 months, but must then be discarded. Keep the ampoules in the outer carton in order to protect from light.
Oxytocin PANPHARMA 10 IU/mL concentrate for solution for infusion	UK MHRA	PANPHARMA, France	PL 44124/0024	1-mL clear glass ampoules	3 years	Store in a refrigerator (2–8°C). Keep the ampoules in outer carton in order to protect from light.
Oxytocin injection, USP (synthetic)	US FDA	West-Ward Pharmaceutical, USA	NDA #018243	1-mL single-dose vial	Not specified	Store at 25˚C; excursions permitted to 15–30˚C [See USP Controlled Room Temperature.]* Do not freeze.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Oxytocin injection USP	US FDA	Fresenius Kabi, USA	NDA #018248	1-mL single-dose vial	Not specified	Store at 20˚–25˚C [See USP Controlled Room Temperature.]* Do not permit to freeze.
Pitocin® (oxytocin injection, USP)	US FDA	Par Sterile Products LLC, USA	NDA #018261	1-mL single-dose vial	Not specified	Store between 20˚ and 25˚C [See USP Controlled Room Temperature.]*
Oxytocin injection, USP	US FDA	Hikma Farmaceutica, USA	ANDA #200219	1-mL single-dose vial	Not specified	Store at 20˚–25˚C [See USP Controlled Room Temperature.]* Do not permit to freeze.
Syntocinon® oxytocin 10 IU/mL injection ampoule	TGA Australia	Viatris Pty Ltd, Australia	AUST R 13383	Clear glass 1-mL ampoule	5 years	Store at 2° to 8°C. Refrigerate. Do not freeze.
Viatocinon oxyotcin 10 IU/mL injection ampoule	TGA Australia	Viatris Pty Ltd, Australia	AUST R 164131	Clear glass 1-mL ampoule	3 years	Store at 2°C to 8°C. Refrigerate. Protect from light. Once removed from refrigerator the ampoules may be stored below 25˚C for up to 4 weeks only, provided that the product is used before printed expiry date. Thereafter, ampoules must be discarded.
Oxyotcin GH solution for injection 10 IU/mL ampoule	TGA Australia	Generic Health Pty Ltd	AUST R 207986	Clear glass 1-mL ampoule	3 years	Store at 2°C–8°C. Refrigerate. Do not freeze. Protect from light.
Oxytocin APX oxytocin 10 IU/mL solution for injection ampoule	TGA Australia	Arrotex Pharmaceuticals Pty Ltd, Australia	AUST R 225656	Clear glass 1-mL ampoule	3 years	Store at 2–8°C (Refrigerate. Do not freeze). Protect from light.

** Please note that this is the storage condition as approved for the US market. Since the room temperatures in low- and middle-income countries often exceed such controlled room temperature, it is recommended oxytocin supplied to those countries be included in the cold chain between 2°C and 8°C and be labeled as such.*

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross-check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedicinfo.ch/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods.

Related products

Other presentations of oxytocin injection on the market include:

- Oxytocin injection 5 IU/mL in 1-mL ampoule
- Oxytocin injection 10 IU/mL in 10-mL multidose vial
- Oxytocin injection 2 IU/2mL in 2-mL ampoule

They are used for the same indications, dosage, and administration. However, it is important to note that the WHO EML recommends oxytocin injection 10 IU in 1-mL presentation for convenient use in prevention and treatment of PPH. According to the WHO recommendations for the prevention and treatment of PPH, for PPH prevention 10 IU is administered as intramuscular or slow intravenous injection and for PPH treatment, 10–40 IU is administered as an intravenous (IV) infusion.

In certain markets, the price of the 5 IU/mL product may be attractive to meet local needs. However, as most dosing regimens for PPH are likely to require more ampoules of 5 IU/mL than 10 IU/mL, the cumulative costs may be substantively higher. It is therefore recommended to procure only oxytocin injection 10 IU/mL.

STORAGE, STABILITY, AND DEGRADATION

Oxytocin degrades when exposed to prolonged heat. It is therefore recommended that oxytocin products be kept refrigerated at 2–8°C. Procurers and health facilities should have adequate cold-chain infrastructure for the transportation and storage of quality oxytocin.

Shelf life: 18–60 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Store in a refrigerator (2–8°C). Do not freeze. Protect from light.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table O-1 and Table O-2 above.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the International Pharmacopeia (IP), US Pharmacopeia (USP), and British Pharmacopeia (BP), depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopeias are similar, except the pH, related substances, and/or bacterial endotoxin limits.

Table O-3. International Pharmacopeia Specifications for Oxytocin Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) TLC	The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.	1.14.1 TLC
b) HPLC	The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.	1.14.4 HPLC
pH	pH of the injection, 3.0 – 5.0	1.13 pH value
Assay	90.0–110.0%	1.14.4 HPLC
Related substances	In the chromatogram obtained with solution (1), the area of not more than one peak, other than the principal peak, is greater than the area of the principal peak obtained with solution (2) (2%). No such peak, other than the principal peak, is greater than 2.5 times the area of the principal peak obtained with solution (2) (5%).	1.14.4 HPLC
Bacterial endotoxins	Less than 0.5 IU of endotoxin per IU of oxytocin	3.4 Test for bacterial endotoxins
Sterility	Sterile	3.2 Test for sterility
Extractable volume	Comply	5.6 Extractable volume for parenteral preparations

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table O-4. US Pharmacopeia Specifications for Oxytocin Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) HPLC	The retention time of the oxytocin peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	USP<621>
Perform one of the following two tests		
b) Nuclear magnetic resonance (NMR)	The NMR spectra from both the standard solution and the test solution are qualitatively and quantitatively similar, and all resonances from the spectrum of the standard solution are present in the spectrum of the test solution and have the same chemical shift values (±0.1 ppm).	NMR
c) Amino acid content	Aspartic acid: 0.90–1.10 Glutamic acid: 0.90–1.10 Proline: 0.90–1.10 Glycine: 0.90–1.10 Leucine: 0.90–1.10 Isoleucine: 0.90–1.10 Tyrosine: 0.7–1.05 Half-cystine: 1.4–2.1 Not more than traces of other amino acids are present.	USP<1052>
pH	3.0–5.0	USP<791>
Assay	90.0–110.0%	HPLC, USP<621>
Bacterial endotoxins	Not more than 35.7 endotoxin unit per USP oxytocin unit	USP<85>
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table O-5. British Pharmacopeia Specifications for Oxytocin Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) TLC	The principal spot in the chromatogram obtained with solution (1) corresponds in position, size, and intensity to that in the chromatogram obtained with solution (2).	As in Appendix III A
Identification b) HPLC	The chromatogram obtained with solution (1) exhibits a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).	As in Appendix III D
pH	3.5–4.5	As in Appendix V L
Assay	90.0–110.0%	HPLC, as in Appendix III D
Related substances	In the chromatogram obtained with solution (1), the area of any secondary peak is not greater than 0.75 times the area of the principal peak obtained with solution (2) (1.5%). The sum of the areas of any secondary peaks is	HPLC, as in Appendix III D

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	not greater than 2.5 times the principal peak obtained with solution (2) (5%).	
Bacterial endotoxins	Comply	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

OXYTOCIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Antepartum

- Induction of labor for medical reasons—for example, in cases of post-term gestation, premature rupture of the membranes, pregnancy-induced hypertension (pre-eclampsia)
- Stimulation of labor in hypotonic uterine inertia
- Early stages of pregnancy as adjunctive therapy for the management of incomplete, inevitable, or missed abortion

Postpartum

- During cesarean section, but following delivery of the child
- Prevention and treatment of postpartum uterine atony and hemorrhage.

Posology, method, and duration of administration

Oxytocin should be administered as an intravenous infusion or, preferably, by means of a variable-speed infusion pump. It can also be given by intramuscular injection, (although intravenous use can produce a more rapid onset of action and allow for better control of dosing).

Attention should be paid to the oxytocin cold chain (i.e. the requirements of a temperature-controlled supply chain).

Induction or enhancement of labor

If vaginal prostaglandins have been used, oxytocin should be started at least 6 hours after use of vaginal prostaglandins. Oxytocin should be administered as an intravenous drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion, it is recommended that 5 units of oxytocin be added to 500 mL of a physiological electrolyte solution (such as sodium chloride 0.9%). For patients in whom infusion of sodium chloride must be avoided, 5% glucose solution may be used as the infusion fluid (see "Special warnings and precautions for use" section below).

To ensure even mixing, the infusion bottle or bag must be turned upside down several times before use. The initial infusion rate should be set at 1 to 4 milliunits/minute (2 to 8 drops/minute).

The infusion rate may be gradually increased at intervals of at least 20 minutes and increments of not more than 1–2 milliunits/minute, until a contraction pattern similar to that of normal labor is established. In pregnancy near term, this can often be achieved with an infusion rate of less than 10 milliunits/minute (20 drops/minute), and the recommended maximum rate is 20 milliunits/minute (40 drops/minute). In the unusual event that higher rates are required, as may occur in the management of fetal death or for induction of labor at an earlier stage of pregnancy when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated oxytocin solution, e.g. 10 units in 500 mL.

When using a motor-driven infusion pump, which delivers smaller volumes than with drip infusion, the concentration suitable for infusion must be calculated according to the specifications of the pump.

With either method of infusion, the frequency, strength, and duration of contractions as well as the fetal heart rate must be carefully monitored throughout the infusion. Once the level of uterine activity is adequate, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity or fetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after a total dose of 5 units, it is recommended that the attempt to induce labor be ceased; it may be repeated on the following day, starting again at an infusion rate of 1 to 4milliunits/minute.

Incomplete, inevitable or missed abortion

The usual dose is 5 units by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes, followed if necessary by an intravenous infusion at a rate of 20 to 40 milliunits/minute.

Caesarean section

The usual dose is 5 units by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes immediately after delivery.

Prevention of postpartum uterine hemorrhage

The usual dose is 10 units by intramuscular or intravenous injection. Alternatively, 5 units can be given by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes after delivery of the placenta. In women given oxytocin for induction or enhancement of labor, the infusion should be continued at an increased rate during the third stage of labor and for the next few hours.

Treatment of postpartum uterine hemorrhage

The usual dose is 10 units by intramuscular or intravenous injection. Alternatively, 5 units can be given by intravenous infusion (diluted in physiological electrolyte solution and administered as a drip infusion or, preferably, by means of a variable-speed infusion pump) over 5 minutes, followed in severe cases by infusion of a solution containing 5 to 20 units of oxytocin in 500 mL of an electrolyte-containing diluent, run at the rate necessary to control uterine atony.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the product
- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress

Any condition in which, for fetal or maternal reasons, spontaneous labor is inadvisable and/or vaginal delivery is contraindicated, such as:

- Significant cephalopelvic disproportion
- Fetal malpresentation
- Placenta previa and vasa previa
- Placental abruption
- Cord presentation or prolapse
- Overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy

- Polyhydramnios
- Grand multiparity
- In the presence of a uterine scar resulting from major surgery, including classical cesarean section.

Oxytocin should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclampsia or severe cardiovascular disorders.

Oxytocin must not be administered within 6 hours after vaginal prostaglandins have been given (see "Interaction with other medicinal products and other forms of interaction" section below).

Special warnings and precautions for use

Attention should be paid to the oxytocin cold chain (i.e. the requirements of a temperature-controlled supply chain).

Oxytocin via intravenous infusion is preferred, as intravenous bolus injection may cause short-lasting hypotension accompanied by flushing and reflex tachycardia.

Induction of labor

The induction of labor by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision.

Oxytocin should not be infused via the same apparatus as blood or plasma, because it is rapidly inactivated by oxytocin-inactivating enzymes.

Cardiovascular disorders

Oxytocin should be used with caution in patients who have a predisposition to myocardial ischemia due to preexisting cardiovascular disease (such as hypertrophic cardiomyopathy, valvular heart disease, and/or ischemic heart disease, including coronary artery vasospasm), to avoid significant changes in blood pressure and heart rate in these patients.

QT syndrome

Oxytocin should be given with caution to patients with known "long QT syndrome" or related symptoms and to patients taking medicines that are known to prolong the QTc interval (see "Interaction with other medicinal products and other forms of interaction" section below).

Use for induction and enhancement of labour

- Fetal distress and fetal death: Excessive doses of oxytocin can result in uterine overstimulation, which may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, or rupture of the uterus. Careful monitoring of fetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.
- Particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.
- Disseminated intravascular coagulation: Rarely, the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (DIC). The pharmacological induction itself and

not a particular agent is linked to such risk. This risk is increased in particular if the woman has additional risk factors for DIC, such as being 35 years of age or over, complications during pregnancy, and gestational age of more than 40 weeks. In these women, oxytocin or any other alternative medicine should be used with care, and the practitioner should be alerted by signs of DIC, such as bleeding from multiple sites, internal bleeding, purpura of extremities, severe malaise and fever.

Intrauterine death

In the case of fetal death in utero or in the presence of meconium-stained amniotic fluid, tumultuous labor must be avoided, as it may cause amniotic fluid embolism.

Water intoxication

Because oxytocin has mild antidiuretic activity, water intoxication associated with hyponatraemia may result from prolonged intravenous infusion at high doses with large volumes of fluid (e.g. in the treatmentof inevitable or missed abortion or in the management of postpartum haemorrhage).

The combined antidiuretic effect of oxytocin and the intravenous fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary edema without hyponatremia.

Features of water intoxication include:

- Headache, anorexia, nausea, vomiting and abdominal pain.
- Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

To avoid this rare complication, the following precautions must be observed whenever high doses of oxytocin are administered over a long time:

- an electrolyte-containing diluent must be used (not glucose);
- the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labor at term);
- fluid intake by mouth must be restricted and a fluid balance chart should be kept, and
- serum electrolytes should be measured when electrolyte imbalance is suspected.

Renal impairment

Caution should be exercised in patients with severe renal impairment because of possible water retention and possible accumulation of oxytocin.

Anaphylaxis in women with latex allergy

There have been reports of anaphylaxis following administration of oxytocin in women with a known latex allergy. Due to the existing structural homology between oxytocin and latex, latex allergy/intolerance may be an important predisposing risk factor for anaphylaxis following oxytocin administration.

Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Prostaglandins and their analogues
Prostaglandins and their analogues facilitate contraction of the myometrium. They should not be used concomitant with oxytocin because oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see "Contraindications" section above).

Note: Misoprostol may be used with oxytocin for the prevention and treatment of postpartum hemorrhage.

Medicines prolonging the QT interval
Oxytocin is potentially arrhythmogenic; concomitant drugs which prolong the QT interval should be used with caution (see "Special warnings and precautions for use" section above).

Other interactions

Inhalation anesthetics
Inhalation anesthetics (e.g., cyclopropane, halothane, sevoflurane, desflurane) have a relaxing effect on the uterus and produce a notable inhibition of uterine tone, which may in turn diminish the uterotonic effect of oxytocin. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

Vasoconstrictors and sympathomimetics
Oxytocin may enhance the vasopressor effects of vasoconstrictors and sympathomimetics, even those contained in local anesthetics.

Caudal anesthetics
When given during or after caudal block anesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

Fertility, pregnancy and lactation

Pregnancy

The induction of labor by means of oxytocin should be attempted only when strictly indicated for medical reasons (see "Special warnings and precautions for use" section above).

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this medicine and its chemical structure and pharmacological properties, it is not expected to present a risk of fetal abnormalities when used as indicated.

Breastfeeding

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because it passes into the alimentary tract where it undergoes rapid inactivation.

Fertility

Animal reproduction studies have not been conducted with oxytocin. The effects of oxytocin on fertility are unknown.

Effects on ability to drive and use machines

Oxytocin can induce labor. Women with uterine contractions should not drive or use machines.

Undesirable effects

As there is wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by intravenous infusion for the induction or enhancement of labor, administration at too high a dose may result in uterine overstimulation, which may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage, or rupture of the uterus.

Undesirable effects in the tables below are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports; frequency not known (cannot be estimated from the available data). The adverse drug reactions (ADRs) tabulated below are based on clinical trial results as well as post-marketing reports.

The ADRs related to post-marketing experience with oxytocin come from spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency—which is therefore categorized as not known. Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Table O-6. Adverse Reactions in Mother

SYSTEM ORGAN CLASS	ADVERSE REACTION
Immune system disorders	Rare: anaphylactic/anaphylactoid reaction associated with dyspnoea, hypotension, or anaphylactic/anaphylactoid shock
Nervous system disorders	Common: headache
Cardiac disorders	Common: tachycardia, bradycardia Uncommon: arrhythmia Frequency not known: myocardial ischemia, electrocardiogram QTc prolongation
Vascular disorders	Frequency not known: hypotension, hemorrhage, angioedema
Gastrointestinal disorders	Common: nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: rash
Pregnancy, puerperium, and perinatal conditions	Frequency not known: uterine hypertonus, tetanic contractions of uterus, rupture of the uterus
Metabolism and nutrition disorders	Frequency not known: water intoxication, maternal hyponatremia
Respiratory, thoracic, and mediastinal disorders	Frequency not known: acute pulmonary edema
General disorders and administration site conditions	Frequency not known: flushing
Blood and lymphatic system disorders	Frequency not known: disseminated intravascular coagulation

Table O-7. Adverse Reactions in Fetus/Neonate

SYSTEM ORGAN CLASS	ADVERSE REACTION
Pregnancy, puerperium, and perinatal conditions	Frequency not known: fetal distress, asphyxia, death
Metabolism and nutrition disorders	Frequency not known: neonatal hyponatremia

Overdose

The fatal dose of oxytocin has not been established. Oxytocin is inactivated by proteolytic enzymes of the alimentary tract. Therefore, it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under the "Special warnings and precautions for use" and "Undesirable effects" sections above. In addition, as a result of uterine overstimulation, placental abruption, and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous intravenous administration of oxytocin, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication, it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of oxytocin injection products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on oxytocin injection.

API

As of June 2022, there is one oxytocin API prequalified by the WHO PQP.

Table O-8. Manufacturer of WHO-Prequalified Oxytocin API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RETEST PERIOD OR SHELF LIFE	DATE OF PRE-QUALIFICATION
WHOAPI-361	Hemmo Pharmaceuticals Pvt. Ltd	Hemmo Pharmaceuticals Pvt. Ltd C-43, MIDC, Off Thane Belapur Road, TTC Industrial Area, Turbhe Navi, Mumbai Dist: Thane Maharashtra 400 613, India	Store in a refrigerator (2°C to 8°C), protect from moisture	36 months	9/25/2019

There are six manufacturers of oxytocin API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal products.

Table O-9. Manufacturers of Oxytocin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Oxytocin (monograph number 780)	Aspen Oss B.V. NL 5349 AB Oss, The Netherlands	R1-CEP 2000-150-Rev 03	04/07/2016	Chemistry
Oxytocin (monograph number 780)	Hemmo Pharmaceuticals Pvt. Ltd. In 400 613 Mumbai, India	R1-CEP 2008-029-Rev 01	9/13/2021	Chemistry

Oxytocin (monograph number 780)	Shanghai Soho-Yiming Pharmaceuticals Co., Ltd. CN 201 707 Chonggu Town, China	R1-CEP 2011-003-Rev 00	8/25/2017	Chemistry
Oxytocin (monograph number 780)	Joint Stock Company "Grindeks" LV 1057 Riga, Latvia	R1-CEP 2002-200-Rev 03	4/25/2022	Chemistry
Oxytocin (monograph number 780)	Shenzhen Jymed Technology Co., Ltd. Cn 518 057 Shenzhen, China	R0-CEP 2015-376-Rev 01	5/28/2020	Chemistry
Oxytocin (monograph number 780	Hybio Pharmaceutical Co., Ltd. Cn 518 057 Shenzhen, China	R0-CEP 2020-322-Rev 00	11/18/2021	Chemistry

Other manufacturers of oxytocin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines. [17]

The specifications of oxytocin API should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP), with additional tests/limits for residual solvents and bacterial endotoxins. If intended for use in the aseptic manufacture of oxytocin injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

Oxytocin is hygroscopic. It should be kept in an airtight container, protected from light, at a temperature of 2–8°C or if sterile, in a sterile, airtight, tamper-evident container.

Excipients

The excipients of oxytocin injection are as follows.[18] There are no special concerns on the excipients.

Table O-10. Excipients of Oxytocin Injection

INGREDIENT	FUNCTION
Acetic acid	pH adjustment
Chlorobutanol	Preservative
Ethanol	Co-solvent
Sodium acetate trihydrate	Buffering agent
Water for injection	Vehicle

Acetic acid is mainly used for pH adjustment. Some formulations may also include sodium hydroxide for such purpose. The pH adjustment is crucial for oxytocin stability because it was shown by Nachtmann et al.[19] that oxytocin is most stable between pH 3 and 5. Hawe et al.[20] also reported that the degradation

[17] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 46th report. Technical Report Series No. 970. Geneva: WHO.

[18] Based on the formulation of an innovator product, Syntocinon®.

[19] Nachtmann, F., K. Krummen, F. Maxl, and E. Reimer. 1981. "Oxytocin. Analytical profiles of drug substances." *Analytical Profiles of Drug Substances* 10: 563–600.

[20] Hawe, A., R. Poole, S. Romeijn Piotr Kasper, R. van der Heijden, and W. Jiskoo. 2009. "Towards Heat-stable Oxytocin Formulations: Analysis of Degradation Kinetics and Identification of Degradation Products." *Pharm Res* 26(7): 1679–88.

of oxytocin was pH- and temperature-dependent and followed (pseudo) first order kinetics. Degradation was fastest at pH 9.0, followed by pH 7.0, pH 2.0, and pH 4.5. Oxytocin degradation in formulations between pH 2.0 and 9.0 follows Arrhenius kinetics, with the pH 4.5 formulation being the most stable. This information is important for formulation development of oxytocin injection.

Chlorobutanol may not be present in some formulations because oxytocin injection 10 IU in 1-mL is intended for a single-dose use, which generally does not require an antimicrobial preservative. However, some manufacturers may add a preservative as an adjunct in aseptic processing of product where there may be product exposure during transfer, filling, packing operations. However, inclusion of the preservative does not compensate for a lower manufacturing standard.

Where chlorobutanol is included in the formulation as an antimicrobial preservative, the amount used should not exceed that used in the comparator products. The amount of preservative should be at the minimum quantity needed to act effectively, and this should be supported by studies. The assay of chlorobutanol (preservative content) should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of chlorobutanol is less than 90.0%, its effectiveness should be established by appropriate studies (e.g., USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP containing a concentration of chlorobutanol corresponding to the lower proposed acceptance criteria.

A single primary-stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

Some manufacturers may claim that chlorobutanol acts as a chemical stabilizer, reducing degradation and allowing the product to be stored at 25˚C. This claim is unfounded.[21]

The oxytocin injection formulation that contains chlorobutanol should also include a buffering agent (e.g. sodium acetate) to maintain the pH since chlorobutanol can hydrolyze when exposed to high temperature and form acidic degradation products.[22] The product should therefore be kept refrigerated to mitigate against oxytocin degradation.

Manufacturing process

Oxytocin injection is a straightforward medicine to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.

The manufacturing process of oxytocin injection is a standard process—conducted under appropriate aseptic conditions—including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, filling and sealing of the ampoules/vials. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

Since oxytocin is susceptible to degradation by heat, terminal steam sterilization cannot be used. Oxytocin injection should be manufactured by aseptic technique for the whole process or sterile filtration of the bulk solution followed by aseptic filling.

---

[21] WHO. 2021. "Regulatory guidance for assessment and management of applications for marketing authorization of oxytocin." Geneva: WHO.

[22] Nair, AD. and Lach, JL. 1959. "The kinetics of degradation of chlorobutanol." *J Am Pharm Assoc* 48: 390–95.

When the aseptic processing is used, all the ingredients must be in sterile grade and comply with the test for sterility before use.

The filters used in the sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components.

Oxytocin injection is prepared by dissolving oxytocin API in the diluent (solution of excipients). Since oxytocin API is hygroscopic (i.e. tend to absorb moisture from the air), it should be kept under the control of relative humidity before introducing into the diluent to avoid degradation. Maintain the temperature of dispensed oxytocin between 2°C and 8°C with the help of frozen-gel ice packs and thermometer in a thermo cool box. The API, after being dispensed, should be used as soon as possible to avoid exposure to light and oxygen.

The selection of the environment temperature conditions may depend on the length of each of the stages of production, the time between stages and how the bulk solution is packed and stored. Suggested conditions for production are at temperatures not more than 25°C.

Nitrogen purging should be carried out throughout the manufacturing and filling process to minimize the contact with atmospheric and dissolved oxygen. If bulk solution storage is required, store the solution under a nitrogen blanket. The lid of the manufacturing tank should be opened and closed immediately after each addition. The temperature of the bulk solution should be maintained below 10°C ± 5°C until filtration.

For the validation of aseptic processing, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

A manufacturing process validation protocol for the validation of the first three production scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. In cases where the manufacturer is already manufacturing production scale batches, full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule or vial should be used.

Suitability of the container should be demonstrated, including the following properties:

Safety

- Glass ampoule/vial must meet compendial requirements such as USP<660> and USP<1660>.

- Rubber stopper (for vial) must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods, such as:

- One-time test reported as part of product development
- Routine leak testing performed as part of the product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as sorption.
- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers, such as PVC, may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Syntocinon® (oxytocin 10 IU/mL injection, Novartis or Sigma Tau, Spain), Pitocin® (oxytocin 10 IU/mL injection, PAR Sterile Products LLC, USA), Oxytocin 10 IU/mL injection (West-Ward Pharmaceuticals Int Ltd, USA), and Oxytocin 10 IU/mL injection (Fresenius Kabi LLC, USA). The composition of the proposed product should be the same as the comparator product.

HEAT-STABLE CARBETOCIN

INJECTION, 100 MICROGRAMS/ML

GENERAL PRODUCT INFORMATION

Postpartum hemorrhage (PPH) is commonly defined as a blood loss of 500 mL or more within 24 hours after birth. PPH is the leading cause of maternal mortality in low- and middle-income countries (LMICs) and the primary cause of nearly one quarter of all maternal deaths globally. The majority of deaths due to PPH could be avoided through the use of prophylactic uterotonics during the third stage of labor and by timely and appropriate management.

Carbetocin is a long-acting synthetic agonist analogue of human oxytocin. It has a greater biological effect and longer half-life than oxytocin.[23] It has been used for the prevention of PPH following Caesarean section births since 1997. The original formulation requires refrigeration.[24]
Recently, a heat-stable formulation of carbetocin was developed to specifically address limitations in refrigeration and cold-chain transport of PPH medications in LMICs. The heat-stable formulation, consisting of 0.1 micrograms/mL carbetocin in sodium succinate buffer, mannitol, and methionine, is stable at temperatures up to 30°C.[25] When used for PPH prevention after vaginal birth, heat-stable carbetocin has demonstrated non-inferiority to oxytocin for the prevention of blood loss of at least 500 mL or the use of additional uterotonic agents.[26]

Heat-stable carbetocin is included on the WHO Model List of Essential Medicines (EML), and in the WHO recommendations on uterotonics for the prevention of postpartum hemorrhage.27 WHO recommends the use of heat-stable carbetocin (100 micrograms/mL, intramuscularly or intravenously), along with misoprostol and ergometrine, for the prevention of PPH for all births in settings where

---

[23] Dell-Kuster, S., Hoesli, I., Lapaire, O. et al. 2016. "Efficacy and safety of carbetocin applied as an intravenous bolus compared to as a short-infusion for caesarean section: study protocol for a randomized controlled trial." *Trials* 17: 155. https://doi.org/10.1186/s13063-016-1285-5.

[24] Widmer, M., Piaggio, G., Abdel-Aleem, H. et al. 2016. "Room temperature stable carbetocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally: study protocol for a randomized controlled trial." *Trials* 17: 143. https://doi.org/10.1186/s13063-016-1271-y

[25] Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

[26] Widmer, M., Piaggio, G., Nguyen, T.M., et al. 2018. "Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth." *New England Journal of Medicine* 379(8): 743-752. doi: 10.1056/NEJMoa1805489

[27] WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1 Last accessed: August 2022

oxytocin is unavailable or its quality cannot be guaranteed, and where its cost is comparable to other effective uterotonics.

It should be noted that the WHO recommendation applies only to the use of carbetocin for the prevention of PPH. Unlike oxytocin, misoprostol and ergometrine, carbetocin is not indicated for treatment of PPH, and it is contraindicated during pregnancy and must not be used for the induction or augmentation of labor.

Heat-stable carbetocin is available under the proprietary names Pabal®, Duratocin®, and Carbetocin Ferring. When cost is a concern, it should be noted that Carbetocin Ferring is made available by Ferring at an affordable and sustainable price for use in public-sector healthcare facilities in LMICs. This price is a subsidized price of $0.31 ± 10% per ampoule of 100 micrograms Carbetocin Ferring, Ex Works.[28] This is comparable to the current United Nations Population Fund (UNFPA) price for oxytocin of $0.33 per unit (10 I.U.), making Carbetocin Ferring a cost-effective option in low-income settings.

KEY CONSIDERATIONS IN PROCUREMENT

1. Only the heat-stable formulation of carbetocin should be procured. Procurers should pay attention to the formulation declared by the manufacturer and product labeling for storage at room temperature (below 30°C).

2. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

3. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use, as carbetocin is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product formulation

The heat-stable formulation differs from the non-heat-stable (refrigerated) formulation only in its excipients. Comparison of the two existing formulations of carbetocin is shown in Table C-1 below.

[28] Ferring Pharmaceuticals. 2020. "Swissmedic approves Carbetocin Ferring for the prevention of postpartum haemorrhage in all births." Available at: https://www.ferring.com/swissmedic-approves-carbetocin-ferring-for-the-prevention-of-postpartum-haemorrhage-in-all-births/ Last accessed: August 2022

Table C-1. Composition of heat-stable carbetocin injection[29]

CARBETOCIN HEAT-STABLE FORMULATION		CARBETOCIN REFRIGERATED FORMULATION	
Component	**Function**	**Component**	**Function**
Carbetocin	Active ingredient	Carbetocin	Active ingredient
Succinic acid	Buffer	Sodium chloride	Isotonicity agent
Mannitol	Isotonicity agent	Glacial acetic acid	pH adjustment
L-methionine	Antioxidant	Water for injection	Solvent
Sodium hydroxide	pH adjustment		
Water for injection	Solvent		

Procurement of carbetocin heat-stable formulation as per the WHO EML is recommended.

Product specification

Heat-stable carbetocin injection products must comply with the quality specifications suggested in "Product Specifications" section below.

Packaging and labeling

Heat-stable carbetocin injection is supplied in single-dose ampoules (e.g. Carbetocin Ferring) and single-dose vials (e.g. Pabal®, Duratocin®) containing 100 micrograms in 1 mL.

The container-closure system (ampoule/vial) must be sufficient to preserve sterility during the shelf life of the product.

Additional information about heat-stable carbetocin injection packaging and labeling can be found in the Annex.

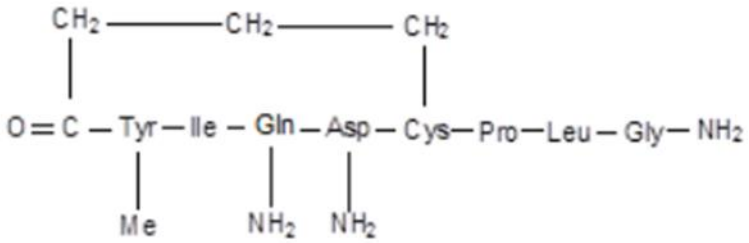
Storage, transportation, and distribution

Heat-stable carbetocin does not need to be maintained in the cold chain, but should be stored below 30°C.

Procurers must ensure that the product is stored safely so that the ampoule/vial cannot break or leak, which would compromise its sterility.

Name of the Medicinal Product	Heat-stable carbetocin injection
Chemical Name	Carbetocin 1-desamino-1-monocarba-2-(0-methyl)-tyrosine oxytocin

[29] Widmer, M., Piaggio, G., Abdel-Aleem, H. et al. 2016. "Room temperature stable carbetocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally: study protocol for a randomized controlled trial." *Trials* 17: 143. https://doi.org/10.1186/s13063-016-1271-y

	Carbetocin is a long-acting synthetic agonist analogue of human oxytocin, with antihemorrhagic and uterotonic activities. Upon administration, carbetocin binds to oxytocin receptors in the uterine smooth muscle, resulting in rhythmic contractions, increased frequency of existing contractions, and increased uterine tone.
Chemical Structure	$C_{45}H_{69}N_{11}O_{12}S$ 
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Heat-stable carbetocin injection contains 100 micrograms of carbetocin per mL. List of typical excipients[30]: ■ L-methionine ■ Succinic acid ■ Mannitol ■ Sodium hydroxide for pH adjustment ■ Water for injection
Packaging and Presentation	The WHO EML states "carbetocin injection (heat stable) 100 micrograms/mL", which does not preclude procurement of any particular presentation of carbetocin. Heat-stable carbetocin injection is packed in glass ampoules or vials.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

30 Based on the formulation of an innovator product, Duratocin® / Pabal®.

WHO-prequalified products

As of August 2022, there is only one heat-stable carbetocin injection product prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

Table C-2. List of WHO-prequalified heat-stable carbetocin injection

WHO REF. NUMBER	RH095
MARKETING AUTHORIZATION HOLDER	Ferring International Center SA, Chemin de la Vergognausaz 50, St Prex, 1162, Switzerland
MANUFACTURING SITE	FPP manufacturing site: - Ferring Pharmaceuticals (China) Co Ltd, No. 6 HuiLing Lu (Ferring Road), National Health Technology Park, Zhongshan City, Guangdong Province, China (People's Republic of) - Steril-Gene Life Sciences (P) Ltd., 45, Mangalam Main Road, Mangalam Village, Villianur Commune, Puducherry, 605 110, India API manufacturing site: PolyPeptide Laboratories France SAS, Buildings 1 and 2, 7 rue de Boulogne, Strasbourg, 67100, France
DOSAGE FORM AND STRENGTH	Solution for injection 100 micrograms/mL
PACKAGING AND PRESENTATION	Ampoule; Type I glass 1 mL x 10’s
DATE OF PRE-QUALIFICATION	July 4, 2022
SHELF LIFE	48 months
STORAGE CONDITION	Do not store above 30°C. Do not freeze. Keep ampoules in the outer carton, in order to protect from light.

SRA-approved products

Table C-3. Examples of SRA-approved heat-stable carbetocin injection

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
PABAL 100 micrograms/mL solution for injection	UK MHRA	Ferring Pharmaceuticals Ltd, UK	PL 03194/0058	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	Keep vials in the outer carton, in order to protect from light. Store below 30°C. Do not freeze.
Carbetocin Ferring Injektionslösung 100 µg/mL	Swissmedic (Switzerland)	Ferring AG, Switzerland	67157	Type I glass ampoule	Not specified	Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.
PABAL Injektionslösung 100 µg/ml	Swissmedic (Switzerland)	Ferring AG, Switzerland	58079	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	Not specified	Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.
PABAL 100 microgrammes/mL, solution injectable	ANSM, France	Ferring SAS, France	34009 550 109 2 0	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	Store the vials in the original outer packaging, in order to protect from light. Store at a temperature not exceeding 30°C. Do not freeze.
PABAL 100 Mikrogramm/mL Injektionslösung	BfArM, Germany	Ferring Arzneimittel GmbH, Germany	64579.00.00	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	The vials should be kept in the original packaging in order to protect the contents from light. Do not store above 30°C. Do not freeze.
Pabal 100 mikrogram/mL injektionsvätska, lösning	MPA, Sweden	Ferring Läkemedel AB, Sweden	24549	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	Store the vials in the outer carton. Sensitive to light. Do not store above 30°C. Do not freeze.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
DURATOCIN solution for injection, 100 micrograms/mL	Health Canada	Ferring INC, Canada	02496526	Colorless glass vials with bromobutyl rubber stoppers and aluminum crimp cap.	Not specified	Store at room temperature (15°C to 30°C).
DURATOCIN 100 micrograms/mL solution for injection	TGA Australia	Ferring Pharmaceuticals Pty Ltd, Australia	AUST R 233671	1 mL clear glass vial with a bromobutyl rubber stopper and an aluminum crimp cap with a tear-off over cap	3 years	Store below 30°C. Once the vial has been opened, the product should be used immediately.

Note: Carbetocin is not available in the United States.

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedicinfo.ch/
- HealthCanada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other presentations of carbetocin injection that exist in the market include:

- Carbetocin 100 micrograms/mL solution for injection in pre-filled glass syringe

It is used for the same indications, dosage and administration. However, it should be noted that carbetocin injection in pre-filled syringe is the non-heat-stable formulation, which contains sodium chloride, acetic acid for pH adjustment, and water for injections. It is typically labeled for storage under refrigerated conditions, between 2–8°C.31

STORAGE, STABILITY, AND DEGRADATION

Shelf life: 36–48 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.

[31] Medicines & Healthcare Products Regulatory Agency (MHRA). 2021. Summary of Product Characteristics of Carbetocin 100 micrograms/mL solution for injection in pre-filled syringe. Available at: https://mhraproducts4853.blob.core.windows.net/docs/a64a13c549a55f490a0b84f6db5be369b52c5a14 Last accessed: August 2022

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table C-2 and Table C-3 above respectively.

Malm et al.32 reported that the main degradation routes of carbetocin are found to be deamidation, oxidation, and racemization. Deamidation of the amide side-chains of asparagine and glutamine and the amidated glycine C-terminus is favored by low pH (acid-catalyzed hydrolysis), and to some extent by high pH (direct base hydrolysis). The thioether linkage is sensitive to oxidation, which is accelerated by increasing pH. The racemization of the asparagine residue from the L to the D-form is an important degradation route at pH-values above ≈ 6. Due to the presence of an antioxidant (methionine) in the heat-stable carbetocin formulation, degradation by oxidation was negligible at all pH-values. The optimum pH where the sum of remaining degradation pathways is minimized was determined to be pH 5.45.

PRODUCT SPECIFICATIONS

There is currently no published pharmacopeial specifications for heat-stable carbetocin 100 micrograms/mL injection. Therefore, the product should meet the in-house specifications established by the manufacturers, which should comply with the ICH Q6A guideline.33 Some general factors that the procurers should consider when assessing the in-house specifications of heat-stable carbetocin injection are highlighted in this section. Additional considerations in quality assessment of heat-stable carbetocin are included in part 2 of the attached Annex.

The minimum parameters to be included in the product specifications of heat-stable carbetocin injection include appearance, pH, identification and assay of active pharmaceutical ingredient (API), impurities, identification and assay of methionine (antioxidant), bacterial endotoxins, sterility, extractable volume and particulate matter.

Due to the lack of compendial methods, any in-house analytical procedures (e.g. HPLC assay and impurity methods) used for routine testing of heat-stable carbetocin injection should be shown to be fully validated.

pH

The study from Malm et al. demonstrated the optimum pH of heat-stable carbetocin to control the amount of impurities as pH 5.45. Heat-stable carbetocin injection can therefore be expected to demonstrate a pH in the region of that value for optimum stability.

Assay of API (carbetocin)

The acceptable limit for the API content in the product release specifications is ± 5% of the label claim (i.e. 95.0–105.0%), whereas it is ± 10% of the label claim (i.e. 90.0–110.0%) in the shelf-life specifications.

---

32 Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

33 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1999. "Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A." Geneva: ICH. Available at: https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf

Impurities

According to the study from Malm et al., known degradation products found in heat-stable carbetocin injection are shown in the below table:

Table C-4. Degradation products of carbetocin

MATERIAL	PATHWAY
[Gly^{9}-OH]carbetocin	Hydrolysis
[Asp^{5}]carbetocin	Hydrolysis
[βAsp^{5}]carbetocin	Hydrolysis
[Glu^{4}]carbetocin	Hydrolysis
Carbetocin sulfoxide isomer 1	Oxidation
Carbetocin sulfoxide isomer 2	Oxidation
[D-Asn^{5}]carbetocin	Racemization

Tests and acceptance limits for those impurities as well as the total impurities should be included in the product specifications.

As carbetocin is a synthetic peptide that is beyond the scope of the ICH Q3B guideline[34], the impurities limits should be set based on thresholds for reporting, identification and qualification of organic impurities described in the European Pharmacopeia (Ph. Eur.) General Monograph 'Substances for Pharmaceutical Use' as follows:

- reporting threshold above 0.10%
- identification threshold above 0.5%
- qualification threshold above 1.0%.

Therefore, any impurities observed above the identification threshold (0.5%) should be identified, and the limits above the qualification threshold (1.0%) should be qualified. A limit of no more than 0.5% for unspecified impurities should be included in the heat-stable carbetocin product specifications. Procurers need to verify from manufacturers that there is satisfactory data to justify the impurities limits.

Identification and assay of methionine

L-methionine is included in the heat-stable formulation of carbetocin as an antioxidant. Identification and content determination tests and limits for methionine should therefore be included in the product specifications, according to the Committee for Medicinal Products for Human Use (CHMP) 'Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product'.35 If the

[34] ICH. 2006. "Impurities in new drug products Q3B(R2)." Geneva: ICH. Available at: https://database.ich.org/sites/default/files/Q3B%28R2%29%20Guideline.pdf

[35] Committee for Medicinal Products for Human Use (CHMP). 2007. "Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product." European Medicines Agency, Amsterdam. (EMEA/CHMP/QWP/396951/2006). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-excipients-dossier-application-marketing-authorisation-medicinal-product-revision-2_en.pdf

lower limit for the proposed acceptance criterion for the assay of methionine is below 90%, the adequacy of the specified limits should be justified on the basis of controlled conditions and stability testing, to ensure that sufficient antioxidant remains to protect the product throughout its entire shelf-life.

Tests required for parenteral product

Heat-stable carbetocin injection is a parenteral product, it should therefore meet pharmacopeial standards for sterility, bacterial endotoxins, and particulate matter as well.

CARBETOCIN ANNEX

PART 1: CLINICAL PARTICULARS[1]

Therapeutic indications

Prevention of postpartum hemorrhage due to uterine atony.

Posology, method, and duration of administration

Posology

Carbetocin must be administered as soon as possible after delivery of the infant and preferably before delivery of the placenta. It should be administered in an obstetric unit by appropriately skilled and trained health care providers

Caesarean section under epidural or spinal anesthesia:

A single dose of 100 micrograms carbetocin (1 mL) by slow intravenous injection (over 1 minute) after delivery of the infant.

There are limited data on the use of carbetocin with general anesthesia.

Vaginal delivery:

A single dose of 100 micrograms (1 mL) by slow intravenous injection (over 1 minute) or by intramuscular injection, after delivery of the infant.

Children and adolescents

Only limited data are available on the safety and efficacy of carbetocin in adolescents after the menarche. In adolescents from the age of 15 years, the same dose as in adults may be administered under adequate supervision, if indicated.

Carbetocin is not recommended in adolescents under 15 years of age, i.e. those who are not yet fully mature, due to lack of data.

There is no indication for use in pre-pubescent children.

Elderly

There is no indication for use in post-menopausal women.

Hepatic or renal impairment

The pharmacokinetics of carbetocin in patients with hepatic or renal impairment have not been investigated. Therefore, carbetocin should not be used in these patients (see "Contraindications" section)

---

[1] Based on Carbetocin Ferring Summary of Product Characteristics published by WHO Prequalification (WHO reference number RH095) Available at: https://extranet.who.int/pqweb/sites/default/files/RH095part4v1.pdf Last accessed: March 2023

Method of administration

For intravenous or intramuscular administration. For intravenous administration carbetocin must be administered slowly, over 1 minute. Carbetocin is for single administration only. No further doses of carbetocin should be administered.

Contraindications

Carbetocin is contraindicated in the following circumstances:

- Pregnancy and labor before delivery of the infant
- For induction or augmentation of labor
- Serious cardiovascular disorders
- Epilepsy
- Renal or hepatic disorders
- Hypersensitivity to carbetocin, oxytocin or to any of the excipients in the product

Special warnings and precautions for use

Carbetocin should be used only in obstetric units by appropriately skilled and trained health care providers.

Persistent or excessive bleeding

If uterine bleeding persists, the cause must be determined. Possible causes are retained placental fragments, injuries to the perineum, vagina or cervix, inadequate emptying or repair of the uterus after caesarean section, or disorders of blood coagulation.

If uterine hypotonia or atonia persists after administration of carbetocin, with consequent excessive bleeding, therapy with another uterotonic can be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persisting uterine atony after oxytocin administration.

Water retention

Animal studies show that carbetocin has some antidiuretic activity (vasopressin activity: <0.025 IU/vial) and there is, therefore, a risk of water intoxication with hyponatremia, especially in patients receiving large volumes of infusion solutions. Attention should be paid to the early signs of water intoxication or hyponatremia – such as drowsiness, listlessness and headache – to prevent complications such as convulsions and coma.
In the presence of migraine, asthma, cardiovascular disease, and other conditions in which a rapid increase in extracellular water may be hazardous for an already overburdened system, carbetocin should only be used after carefully weighing up of the benefits and risks and under appropriate supervision.

Cardiac risks (including QT prolongation)

Adverse cardiac effects such as bradycardia, QT prolongation, arrhythmias, and myocardial ischemia have occurred with oxytocin, especially after rapid intravenous injection. It is not known if these effects are caused by oxytocin treatment or were caused by other simultaneously administered medicines. There are no data on a possible pathophysiological mechanism. Because carbetocin is structurally closely related to oxytocin, carbetocin should be used with special caution in patients with long-QT

syndrome or other risk factors for QT prolongation (such as co-medication with drugs with a risk of QT-prolongation).

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100-microgram ampoule, that is to say it is essentially 'sodium-free'.

Further precautions

Carbetocin has not been investigated in patients with eclampsia. It should therefore be used with special caution in cases of eclampsia or pre-eclampsia, and patients should be carefully monitored.
Only limited data are available on the use of carbetocin in patients with (gestational) diabetes.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been undertaken with carbetocin.

There is a risk of a cumulative effect with the use of methylergometrine or oxytocin after the administration of carbetocin.

During clinical trials, carbetocin has been administered in association with a number of analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anesthesia. No drug interactions were observed.

The following interactions have occurred involving oxytocin. Since carbetocin is structurally related to oxytocin, they might also occur with carbetocin:

■ Prostaglandins potentiate the effect of oxytocin. Therefore, prostaglandins should not be used at the same time as carbetocin. If simultaneous use cannot be avoided, then the patient must be closely monitored.

■ Inhalation anesthetics, e.g. halothane, can potentiate the hypotensive effect and reduce the effect of carbetocin on the uterus. In case of concomitant use of such anesthetics with oxytocin, arrhythmias have also been reported

■ Hypertension has been reported when oxytocin was given 3 to 4 hours after a vasoconstrictor was administered in conjunction with caudal-block anesthesia.

Carbetocin can potentiate the hypertensive effect of ergot-alkaloids such as methylergometrine.

Fertility, pregnancy and lactation

Pregnancy

Carbetocin is contraindicated during pregnancy and must not be used for the induction of labor (see "Contraindications" section above).

Breastfeeding

No relevant effects on milk let-down have been reported during clinical trials. Small amounts of carbetocin have been detected in breast milk of nursing women. The small amounts of carbetocin transferred into colostrum or breast milk after a single injection of carbetocin, and subsequently

ingested by the infant, are likely to be degraded by enzymes in the gastrointestinal tract and therefore have probably no clinically relevant effects in the breastfed infant.

Breast-feeding can be started without restrictions after the use of carbetocin.

Effects on ability to drive and use machines

No studies of the effect on the ability to respond, to drive and to use machines have been conducted. However, carbetocin can have undesirable effects such as dizziness that could impair the ability to drive.

Undesirable effects

The following statements are based on clinical trials in which carbetocin was used in the context of a Caesarean section. However, a similar safety profile is to be expected on use after vaginal delivery. The undesirable effects observed with carbetocin during the clinical trials after vaginal delivery were also comparable in frequency and severity to those of oxytocin.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as very common (at least 1 in 10); common (1 in 100 to 1 in 10); uncommon (1 in 1000 to 1 in 100); rare (1 in 10,000 to 1 in 1000); or very rare (less than 1 in 10,000).

Table C-5. Adverse events observed with carbetocin

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Blood and lymphatic system disorders	Common: anemia
Immune system disorders	Not known: hypersensitivity reactions (including anaphylactic reactions)
Nervous system disorders	Very common: headache, tremor Common: dizziness
Cardiac disorders	Uncommon: tachycardia (see also "Special warnings and precautions for use" section above)
Vascular disorders	Very common: hypotension, flushing
Respiratory, thoracic, and mediastinal disorders	Common: dyspnea
Gastrointestinal disorders	Very common: nausea, abdominal pain Common: metallic taste, vomiting
Skin and subcutaneous tissue disorders	Very common: pruritus
Musculoskeletal and connective tissue disorders	Common: back pain
General disorders and administration site conditions	Very common: feeling of warmth Common: chills, pain, chest pain, sweating

Reactions at the administration site were not specifically investigated. As with other drugs, local irritation is likely, especially with intramuscular administration.

Overdose

An overdose with uterotonic agents such as carbetocin can induce uterine hyperactivity. Symptoms of an overdose observed with oxytocin are also likely with carbetocin. If carbetocin is used before delivery of the infant (see "Contraindications" section),hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions can occur, with the risk of uterine rupture or increased postpartum hemorrhage.

An overdose may lead to hyponatremia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake.

Treatment of overdosage consists of symptomatic and supportive therapy. If signs or symptoms of overdosage occur, oxygen should be given. In the case of water intoxication, it is important to restrict fluid intake, initiate diuresis, correct electrolyte disturbances, and control convulsions if they occur.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of heat-stable carbetocin products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on heat-stable carbetocin injection.

API

As of August 2022, there is no carbetocin API prequalified by the WHO PQP. Certificate of suitability to monographs of the European Pharmacopeia (CEP) is not applicable since no Ph. Eur. monograph exists for carbetocin.

The WHO-prequalified heat-stable carbetocin injection (Carbetocin Ferring) has used carbetocin API manufactured by PolyPeptide Laboratories France SAS.2 This manufacturer can be considered as a trusted source as it has passed the assessment of WHO PQP team. However, it is recommended to check for updated information on the WHO PQP website at the time of quality assessment. Other manufacturers of carbetocin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines3 to support the quality assessment.

There is currently no published pharmacopeial specifications for carbetocin API. Therefore, in-house specifications should be established by the manufacturers and adhere to the ICH Q6A guideline. The typical specifications of carbetocin API include the following parameters: identification, assay, related substances, specific optical rotation, water content, acetic acid content, residual solvents, microbial limits, and bacterial endotoxins.4 If intended for use in the aseptic manufacture of heat-stable carbetocin injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

According to Malm et al.,5 [D-Cys6]carbetocin and [des-Gln4]carbetocin are known synthesis-related impurities of carbetocin API. They should therefore be appropriately controlled in the specifications of carbetocin API. Furthermore, any impurities above the identification threshold given in the Ph. Eur. General monograph 'Substances for pharmaceutical use' (0.5%) should be identified, and the limits above the qualification threshold (1.0%) should be qualified. A limit of not more than 0.5% for unspecified impurities should be included in the carbetocin API specifications.

Carbetocin is hygroscopic.6 It should be stored in a tightly closed original container at 2–8°C and avoid exposure to light,7 or in the conditions recommended by the API manufacturer.

---

[2] WHO. 2022. Prequalified medicinal products: RH095. Available at: https://extranet.who.int/pqweb/medicine/4419 Last accessed: August 2022

[3] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.

[4] PolyPeptide Group. 2021. Carbetocin drug substance specification. Available at: https://www.polypeptide.com/wp-content/uploads/2018/09/Carbetocin-web-spec-2021.pdf Last accessed: August 2022

[5] Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

[6] https://www.trc-canada.com/product-detail/?C175925 Last accessed: August 2022

[7] PolyPeptide Group. 2019. Carbetocin safety data sheet. Available at: https://www.polypeptide.com/wp-content/uploads/2018/09/Carbetocin-SDS-v10-UK.pdf Last accessed: August 2022

Excipients

The typical excipients of heat-stable carbetocin injection are shown in the table below.8 There are no special concerns with the excipients. No excipient with the risk of transmitting TSE/BSE is used.

Table C-7. Excipients of heat-stable carbetocin injection

INGREDIENT	FUNCTION
L-methionine	Antioxidant
Succinic acid	Buffer agent
Mannitol	Isotonicity agent
Sodium hydroxide	pH adjustment
Water for injection	Solvent

Excipients should be controlled according to the requirements of the officially recognized compendial standard (Ph.Int., Ph.Eur./BP, USP), and include a test for bioload or bacterial endotoxins.

If excipients not contained in the innovator product are used in any generic products, it is necessary to demonstrate compatibility with the carbetocin API through chromatographic results (assay, purity). The choice of excipients, their concentration and their characteristics can influence the heat-stable carbetocin product performance and therefore should be discussed relative to their respective functions.

Manufacturing process

The manufacturing process of heat-stable carbetocin injection is a standard process—conducted under appropriate aseptic conditions—including the solution preparation steps with adjustment of pH, pre- and sterile filtration, filling and sealing of the ampoules/vials. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

The pH adjustment is crucial for heat-stable carbetocin stability because it was shown by Malm et al.9 that carbetocin is most stable at pH 5.45 with low degradation (≤ 4%) after 12 months at 40°C/75% RH. Carbetocin was found to degrade mainly by deamidation of the glutamine residue and the amidated glycine C-terminus at pH-values below the optimum and by racemization of the asparagine residue at pH values above the optimum.

The filters used in the sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components.

The selection of the environment temperature conditions may depend on the length of each of the stages of production, the time between stages and how bulk solution is packed and stored.

Nitrogen purging should be carried out throughout the manufacturing and filling process to minimize contact with atmospheric and dissolved oxygen. If bulk solution storage is required, store the solution under a nitrogen blanket. The lid of the manufacturing tank should be opened and closed immediately after each addition.

---

8 Based on formulation of an innovator product, , Duratocin® / Pabal®.

9 Malm, M., Madsen, I., Kjellström, J. 2018 “Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries.” *J Pept Sci* 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

Heat-stable carbetocin injection may be manufactured by aseptic technique for the whole process. When aseptic processing is used, all the ingredients must be sterile grade and comply with the test for sterility before use.

For the validation of aseptic processing, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

A manufacturing process validation protocol for the validation of the first three production scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. In cases where the manufacturer is already manufacturing production scale batches, full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule or vial should be used.

Suitability of the container should be demonstrated, including the following properties:

Safety

- Glass ampoule/vial must meet compendial requirements such as USP<660> and USP<1660>.
- Rubber stopper (for vial) must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:

- One-time test reported as part of product development
- Routine leak testing performed as part of product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as sorption.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Pabal® (carbetocin 100 micrograms/mL injection, Ferring) and Duratocin® (carbetocin 100 micrograms/mL injection, Ferring). The composition of the proposed product should be the same as the comparator product.

Equivalence of any generic heat-stable carbetocin products with the comparator product should be demonstrated, and the applicant should provide comparative results of physicochemical properties (e.g. pH, density, osmolarity etc.) for both the generic and comparator products.

MISOPROSTOL

TABLETS, 200 MICROGRAMS

GENERAL PRODUCT INFORMATION

Misoprostol is a synthetic analog of a natural prostaglandin E1. It has been widely approved for treatment and prevention of peptic ulcer disease for over a decade before it was investigated as a uterotonic and oxytocic agent. As a result, misoprostol is currently used for two distinct purposes:

- Gastroprotection and healing of peptic and duodenal ulcers
- A variety of obstetric and gynecological indications, including medical abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and prevention and treatment of PPH

Misoprostol is considered an essential medicine by the UN Commission on Life-Saving Commodities for its PPH indication because PPH is the leading cause of maternal death. This document therefore focuses on misoprostol for its use in PPH only.

The WHO's Essential Medicine List (EML) recommends using misoprostol for preventing and treating PPH when oxytocin is unavailable or cannot be administered safely. Although oxytocin injection is the recommended medicine for the prevention and treatment of PPH, the limitations of oxytocin are that it requires a cold chain and skilled administration to deliver effective results. These two conditions cannot always be met in low-resource settings. Misoprostol does not need cold chain storage and its simple tablet form facilitates its use by community health workers and traditional birth attendants. The drug's ease of use and stability at room temperature make it suitable for delivery in low-resource settings. It is therefore recommended as an alternative to oxytocin in the prevention and treatment of PPH where oxytocin use is not feasible or safe.

Furthermore, the WHO recent guideline recommends advance misoprostol distribution to pregnant women for self-administration for prevention of PPH in settings where women give birth outside of a health facility and in the absence of skilled health personnel, provided that appropriate monitoring and evaluation is implemented.[1]

[1] WHO. 2020. "WHO recommendation on advance misoprostol distribution to pregnant women for prevention of postpartum hemorrhage." Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/336310/9789240013902-eng.pdf?sequence=1&isAllowed=y

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

2. The procurer must obtain evidence of the quality, and in particular, the stability of the product from the manufacturer before ordering as the use of inappropriate excipients or inadequately controlled environmental conditions can increase exposure to moisture and cause product degradation. Pre-shipment testing is pointless for inappropriately manufactured and packaged product—the product may comply with specifications shortly after manufacturing but may only have 50 percent of labeled content within six months.

KEY QUALITY CONSIDERATIONS

Product specification

Misoprostol finished product must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

The packaging requirement for misoprostol is double-aluminum blister packs. Packaging is critical for the stability of misoprostol; double-aluminum blister packs effectively protect the products from moisture and prevent degradation.

Products presented in PVC or PVDC/aluminum blister packs should never be purchased because PVC or PVDC/aluminum do not provide adequate protection against penetration by moisture.

When procuring SRA-approved products, the suitability of packaging for the intended markets should be reassessed. For example, some misoprostol products approved in SRA markets (climatic zone II) are packaged in plastic bottles, which is not suitable for use in countries in climatic zones III and IV with high temperature and humidity.

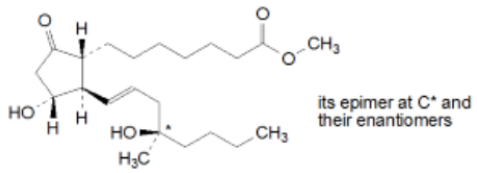
Procurers should ensure that package inserts of the products eligible for procurement include information on the PPH indications and dosages. This is particularly important because the dose for PPH prevention (400-600 micrograms) and treatment (800 micrograms) are significantly higher than the dose for induction which is 25 micrograms. The most common presentation of misoprostol is a 200 mcg. tablet which cannot be safely broken to create a 25 mcg. dose. For induction, a 25 mcg. tablet should be procured or a 200 mcg tablet dissolved in sterile water and titrated to oral dose. Misoprostol has a variety of obstetric and gynecological indications, including PPH. However, only a few products are registered for those indications. Many misoprostol products are registered for gastric ulcer uses and manufacturers' package inserts do not provide information specific for the PPH indication.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Misoprostol tablets are stable at room temperature and do not require cold chain storage. However, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablet form.

Additional information about the misoprostol finished product storage requirement can be found in the "Storage, Stability and Degradation" section below.

Name of the Medicinal Product	Misoprostol
Chemical Name	(±) methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.
Chemical Structure	$C_{22}H_{38}O_5$ 
Pharmaceutical Form	For use in the prevention and treatment of PPH, misoprostol is available in an oral tablet form, which can be administered orally or sublingually.
Qualitative and Quantitative Composition	Each tablet contains 200 micrograms (mcg) of misoprostol. List of typical excipients[2]: – Microcrystalline cellulose – Hydrogenated castor oil – Sodium starch glycolate – Hypromellose
Packaging and Presentation	Typically, cold-form double-aluminum blister (Alu/Alu) is used for primary packaging. Secondary packaging is normally suitable cardboard to protect from damage.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers

[2] Based on the formulation of an innovator product, Cytotec®.

> approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of June 2022, three misoprostol 200 mcg tablets are prequalified by the WHO PQP, as shown below. It is recommended to check the updated information at the time of procurement, which can be found at: https://extranet.who.int/pqweb/content/prequalified-lists/medicines

Table M-11. List of WHO Prequalified Misoprostol Tablets

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH039	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	FPP manufacturing site: Cipla Ltd, Unit 8, Plot No. L-139, S-103 and M-62, Verna Industrial Estate, Salcette, Goa, 403 722, India API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 4x1, 4x7, 4x15	8-Apr-14	2 years	Do not store above 30°C.
RH048*	China Resources Zizhu Pharmaceutical Co Ltd, No 27 Chaoyang North Road, Chaoyang District, Beijing, 100024, China	FPP manufacturing site: China Resources Zizhu Pharmaceutical Co Ltd, No. 27 Chaoyang North Road, Chaoyang District, Beijing, 100024, China API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 3x1, 4x1	22-Nov-16	2 years	Do not store above 30°C.
RH056*	Acme Formulation Pvt. Limited, Hormone Block, Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh, 174101, India	FPP manufacturing site: Acme Formulation Pvt. Ltd, Hormone Block, Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh, 174101, India API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 10x10	27-Apr-16	2 years	Do not store above 30°C; protect from light.

** Include the indication for PPH.*

SRA-approved products

Table M-12. Examples of SRA-Approved Misoprostol 200 mcg Tablets

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Cytotec 200 mcg tablets*	UK MHRA	Pfizer Limited	PL 00057/0956	Oral tablet; cold-formed aluminum blister pack	3 years	Do not store above 30°C. Store in the original package to protect from moisture.
Cytotec*	US FDA	Pfizer	NDA #019268	Oral tablet; bottle	Not specified	Store at or below 25°C, in a dry area.
Misoprostol*	US FDA	Novel Labs Inc.	ANDA #091667	Oral tablet; bottle	Not specified	Store at 20–25°C. [See USP controlled room temperature.] Store in a dry area.
GyMiso 200 mcg, comprimé**	ANSM, France	Linepharma, France	34009 362 499 4 3	Oral tablet; blister pack (Paper/PE/ Aluminum)	2 years	Store at a temperature not exceeding 25°C
Cytotec tablets (misoprostol 200 mcg)*	Swissmedic	Pfizer AG	46945	Oral tablets; not specified	Not specified	Store at room temperature (15-25°C).
Cytotec misoprostol 200 mcg tablet blister pack*	TGA Australia	Pfizer Australia Pty Ltd	AUST R 63983	Oral tablet; cold formed Alu/Alu blister pack	3 years	Store below 25°C; protect from moisture.
Cytotec misoprostol 200 mcg tablet bottle—EX (export only)*	TGA Australia	Pfizer Australia Pty Ltd	AUST R 46849	Oral tablet; bottle	3 years	Store below 30°C
GyMiso misoprostol 200 mcg oral tablet blister pack***	TGA Australia	MS Health Pty Ltd	AUST R 188015	Oral tablet; Alu/Alu blister pack	2 years	Store below 25°C in the original packaging.

** Registration for gastrointestinal indications.*
*** Registration for the indications of medical interruption of intrauterine pregnancy, in combination with mifepristone; and preparation of the cervix before surgical interruption of pregnancy during the first trimester.*
**** Registration for the indication of medical termination of a developing intrauterine pregnancy, in sequential combination with mifepristone.*

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: Error! Hyperlink reference not valid.https://www.swissmedicinfo.ch/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods.

Related products

Other formulations of misoprostol that exist in the market include the following products:

Vaginal tablet 25 mcg	Included in the WHO EML, only for use for induction of labor where appropriate facilities are available.
Misoprostol oral tablet 100 mcg	Indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of complications from gastric ulcer; for example, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.
Misoprostol oral tablet 400 mcg (e.g., Topogyne®, Misoone®)	Indicated for medical termination of developing intrauterine pregnancy, in sequential use with mifepristone.
Misoprostol vaginal 200 mcg vaginal delivery system (e.g., Mysodelle®, Misodel®)	A controlled release formulation that releases misoprostol at a rate of approximately 7 micrograms/hour over a period of 24 hours Indicated for induction of labor in women with an unfavorable cervix, from 36 weeks gestation, in whom induction is clinically indicated.

Combination pack of mifepristone and misoprostol (e.g., Medabon®, MS-2 Step)	Included in the WHO EML, only for use for medical abortion where permitted under national law and where culturally acceptable Consists of 1 tablet of mifepristone 200 mg tablet and 4 tablets of misoprostol 200 mcg tablet

It is important to note that for the PPH indication the WHO EML recommends the use of misoprostol 200 mcg tablets for convenient use in accordance with the dosing regimens. WHO recommends 400 mcg or 600 mcg orally for the prevention of PPH, [1] and sublingual misoprostol at 800 mcg for controlling PPH[2] when oxytocin is unavailable (or its quality cannot be guaranteed) or skilled health personnel are not present to administer injectable uterotonics.

STORAGE, STABILITY, AND DEGRADATION

Misoprostol tablets are stable at room temperature and do not require cold chain storage. However, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablets.

Misoprostol turns into three main inactive degradation products: type A, type B, and 8-epimer misoprostol. The inactive type A misoprostol occurs by dehydration, which produces water. The 8-epi misoprostol is obtained by isomerization. These degradation processes are catalyzed by the presence of water. The type B misoprostol is the result of isomerization of the inactive type A. The rate of degradation increases as water content increases.

It is therefore important to exclude water (moisture) at all stages of the manufacturing process and during storage of the product to ensure that the product will be stable throughout its shelf life. Critical factors related to exclusion of moisture include:

- Selection of API
- Selection of excipients
- Production environment (temperature and relative humidity)
- Packaging

Packaging is very important for the stability of misoprostol. A study of the quality of misoprostol sampled in the field[3] has shown that misoprostol tablets packaged in PVC-aluminum blisters are likely to degrade more rapidly than those packaged in aluminum-aluminum blisters, especially under conditions of high temperature and humidity.

Misoprostol tablets in certain low- and middle-income countries are likely to be subjected to conditions of high humidity and temperature. Therefore, misoprostol tablets should be packed in an aluminum-aluminum blister pack to reduce the risk of exposure to moisture in humid environments.

[1] WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1
[2] WHO. 2012. "WHO recommendations for the prevention and treatment of postpartum hemorrhage." Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf
[3] WHO. 2016. "Quality of Misoprostol Products." In: *WHO Drug Information.* Vol. 30, No. 1. Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/331040/DI301-35-39-eng.pdf?sequence=1&isAllowed=y

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30˚C.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Tables M-1 and M-2, respectively.

PRODUCT SPECIFICATIONS

The product must meet the International Pharmacopeia specifications,[4] or the equivalent thereof.

Table M-13. International Pharmacopeia Specifications for Misoprostol Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification* a) HPLC	The retention time of the principal peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to misoprostol in the chromatogram obtained from solution (2).	1.14.4 High-performance liquid chromatography
Identification* b) TLC	The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).	1.14.1 Thin-layer chromatography
Dissolution	The amount in solution is not less than (NLT) 80% (Q) of the amount declared on the label.	5.5 Dissolution test for solid oral dosage forms
Related substances**	In the chromatogram obtained with solution (1): – The sum of the areas of any peak corresponding to impurity A, B, and E is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%). – The area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%). – The area of any peak corresponding to impurity D is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).	1.14.4 High-performance liquid chromatography
Assay***	90.0–110.0%	1.14.4 High-performance liquid chromatography
Uniformity of content	Each single unit contains within ±15% of the average amount of the active ingredient. However, if one individual unit deviates by more than ±15% but is within ±25% of the average amount of the active ingredient, examine a further 20 units drawn from the same original sample as the first 10 units. The preparation under test complies only if the amount of active ingredient found in	5.1 Uniformity of content for single-dose preparations

[4] As of June 2022, there are no monographs of misoprostol tablets published in the US or British Pharmacopeia; please check for updated information.

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	no more than one out of 30 units deviates by more than ±15% of the average amount. None deviates by more than ±25% of the average amount.	

** Either test A or B may be applied.*

*** Impurity A = 8-epi-misoprostol*
Impurity B = 12-epi-misoprostol
Impurity C = misoprostol A
Impurity D = misoprostol B
Impurity E = Methyl rac-(13E,16RS)-11α,16-dihydroxy-16,18-dimethyl-9-oxo-20-norprosta-13,17-dien-1-oate (mixture of 4 stereoisomers)

**** It is acceptable to use the average of the 10 individual results obtained in the test for "uniformity of content."*

MISOPROSTOL ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Misoprostol is used for a variety of obstetric and gynecological indications:

- Prevention and treatment of PPH where oxytocin is not available or cannot be safely used.
- Management of incomplete abortion and miscarriage.
- First-trimester abortion: misoprostol in combination with mifepristone is indicated for the medical termination of intrauterine pregnancy. The duration of pregnancy for which the product is approved may be different in different countries.
- Cervical ripening: cervical ripening prior to uterine instrumentation; cervical ripening for induction of labor in case of a live fetus and intrauterine fetal death.

It is also indicated for gastroprotection and healing of peptic and duodenal ulcers.

Posology, method, and duration of administration[51,52]

Table M-14. Misoprostol Dosage Based on Indication

INDICATION	DOSAGE	NOTES
PPH prevention	400 or 600 mcg orally single dose	– Included in the WHO EML. – Exclude second twin before administration.
PPH treatment	800 mcg sublingually single-dose	– Included in the WHO EML.
Incomplete abortion	<14 weeks: 600 mcg orally single-dose or 400 mcg sublingually single-dose ≥14 weeks: 400 mcg sublingually, vaginally or buccally 3-hourly (providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision)	– Included in the WHO EML.
Missed abortion (<14 weeks)	800 mcg vaginally, sublingually or buccally (repeated doses can be considered when	– Ideally used at least 24 hours after mifepristone 200 mg.

[51] WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1

[52] WHO. 2022. "Abortion care guideline." Geneva: WHO. Available at https://www.who.int/publications/i/item/9789240039483

INDICATION	DOSAGE	NOTES
	needed to achieve success of the abortion process)	
Induced abortion (<12 weeks)	800 mcg vaginally, sublingually or buccally (repeated doses can be considered when needed to achieve success of the abortion process)	– Ideally used 24–48 hours after mifepristone 200 mg.
Induced abortion (≥12 weeks)	400 mcg vaginally, sublingually or buccally 3-hourly (providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision)	– Ideally used 24–48 hours after mifepristone 200 mg.
Intrauterine fetal demise (≥14 to ≤28 weeks)	400 mcg sublingually or vaginally every 4–6 hours (providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision)	– Ideally used 24–48 hours after mifepristone 200 mg.
Induction of labor (third trimester)	25 mcg vaginally 6-hourly or 25 mcg orally 2-hourly or 25 mcg dissolved in 200 mL water, 25 mL given hourly	– Included in the WHO EML. – Make sure to use the correct dosage—overdose can lead to complications. – Do not use in women with previous cesarean section.
Cervical ripening prior to instrumentation (first trimester)	400 mcg sublingually 1–2 hours before procedure or 400 mcg vaginally or buccally 2–3 hours before procedure	– Use for insertion of intrauterine device, surgical termination of pregnancy, dilatation and curettage, and hysteroscopy. – The sublingual route is more effective for misoprostol administration

Contraindications

- Hypersensitivity to misoprostol or to any of the excipients in the product
- Known allergy to prostaglandins

Contraindications in abortion setting

- Inherited porphyria
- Chronic or acute adrenal or hepatic failure
- Known or suspected ectopic pregnancy

Special warnings and precautions for use

Caution is warranted in women with preexisting heart disease or cardiovascular risk factors, as cardiovascular events have been reported in association with misoprostol.

Caution and clinical judgment are required for women using corticosteroids long term, and for those who have bleeding disorders or severe anemia.

When misoprostol is used for induction of labor, the mother and her fetus should be closely monitored immediately after it is given.

When misoprostol is used for abortion, women should be advised to return for follow-up if they are experiencing signs of ongoing pregnancy.

Misoprostol should not be used in children below pubertal age.

This medicinal product contains hydrogenated castor oil. This may cause stomach upset and diarrhea.

Interaction with other medicinal products and other forms of interaction

Interaction studies show that the pharmacokinetics of propranolol and diazepam are not influenced by concomitant administration of misoprostol.

Misoprostol does not change the pharmacokinetics of antipyrine, suggesting that it does not induce hepatic enzymes.

In a pivotal study performed with misoprostol, no adverse events that would suggest the existence of an interaction between misoprostol and oxytocin were reported in women exposed to prophylactic oxytocin (intramuscular or intravenous) prior to administration of misoprostol.

Combination with nonsteroidal anti-inflammatory drugs

Theoretically, concomitant use with nonsteroidal anti-inflammatory drugs (NSAIDS) may reduce the efficacy of misoprostol. However, no clinically meaningful effect has been shown upon co-administration.

Fertility, pregnancy and lactation

Pregnancy

Misoprostol must not be used during intact pregnancy in the first trimester when the intent is to proceed, as a risk of fetal malformation cannot be excluded when misoprostol is administered during pregnancy.

In a few cases where misoprostol was self-administered (orally or vaginally) during early pregnancy, the following deleterious effects have been observed: malformations of limbs, abnormal fetus movements and cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Animal studies have not demonstrated teratogenicity but have shown fetotoxicity at high doses.

Available data regarding a potential risk of fetal abnormality after an unsuccessful medical abortion are limited and inconclusive; therefore, it is unnecessary to insist on termination of an exposed pregnancy if the woman wishes to continue it. Women should, nevertheless, be informed that due to the unknown risk to the fetus of abortifacient medicines, follow-up is important.

Breastfeeding

The levels of misoprostol in breast milk are low and decline very rapidly: after 5 hours of a single oral dose of 600 mcg, the levels in breast milk are unmeasurable and the risk to the infant is therefore minimal after a single dose. In practical terms, breast-feeding can be continued.

Fertility

Adverse effects on male or female fertility or reproduction were observed in rats at doses much higher than the maximum recommended human dose. Adverse effects on fertility or reproduction in humans seem unlikely.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Headache, dizziness, and tiredness have been reported during treatment with misoprostol. Patients should be instructed that, if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment are shivering and fever. In general, shivering and fever occur 60–90 minutes after misoprostol administration and are transient and short-lived.

List of adverse reactions

Safety of a misoprostol formulation has been evaluated in 1,428 women treated for PPH.

The adverse reactions reported in the clinical program are provided below and are classified according to frequency and system organ class. Undesirable effects are ranked under headings of frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency groupings are as follows:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000),
- Frequency not known (cannot be estimated from available data)

Table M-15. Adverse Reactions from Misoprostol

MEDRA SYSTEM ORGAN CLASS	ADVERSE REACTIONS (FREQUENCY)			
	VERY COMMON	COMMON	UNCOMMON	RARE
Nervous System Disorders		Headache Fainting/Dizziness		
Gastrointestinal Disorders	Nausea	Vomiting/Diarrhea		
Skin and subcutaneous tissue disorders				Allergic reaction

General disorders and administration site disorders	Shivering Fever, including temperature ≥40°C.	Chills	Fatigue

When used for induction of labor, uterine hyperstimulation and rupture as well as fetal distress may occur.

When used for abortion the following adverse events were reported:

- Uterine cramping, prolonged menstrual-like bleeding, on average for nine days (up to 45 days), incomplete abortion. Rarely, genital tract infection and uterine rupture.

Women should be advised to return for follow-up if they are experiencing prolonged heavy bleeding or fever.

Overdose

Symptoms linked to overdose of misoprostol are fever, blood pressure disorders, nausea, abdominal cramping and tremors. There is no known antidote for misoprostol overdose. In the event of an overdose, the patient should be closely monitored.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of misoprostol products. When assessing the complete quality/CMC documentation, assessors should consider the following information on misoprostol tablets.

API

Misoprostol API is viscous oil, which must be stored below -20°C. It is extremely susceptible to degradation. Research established that a dispersion of misoprostol in hydroxypropyl methyl cellulose (HPMC) was considerably more stable than the pure misoprostol oil. Conventional tablets can be prepared from the solid misoprostol dispersion, with a shelf life of several years at room temperature.

As of June 2022, only one manufacturer of misoprostol dispersion (1:100 in HPMC) has been prequalified by the WHO PQP.

Table M-16. Manufacturer of WHO-Prequalified Misoprostol API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RE-TEST PERIOD OR SHELF-LIFE	DATE OF PRE-QUALIFICATION
WHOAPI-226	Piramal Healthcare UK Ltd	Piramal Healthcare UK Ltd Whalton Road Morpeth Northumberland NE61 3YA, UK	Store in a refrigerator (2°C to 8°C), protect from moisture, protect from light	60 months	12/17/2015

Only one manufacturer of misoprostol API has obtained the certificate of suitability to monographs of the European Pharmacopeia (CEP), confirming its suitable quality for use in medicinal product.

Table M-17. Manufacturer of Misoprostol API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Misoprostol (monograph number 1731)	Piramal Healthcare UK Ltd GB NE61 3YA Morpeth, UK	R1-CEP 2010-121-Rev 01	1/20/2017	Chemistry

Other manufacturers of misoprostol API should provide evidence for GMP compliance and API quality documentation as per the WHO guidelines.[53]

The specifications of misoprostol API should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP). The specifications of misoprostol dispersion should be in line with a pharmacopeial monograph (Ph.Int. or USP).

Excipients

Excipients must conform to pharmacopeia monographs. The recommendations for the selection of key excipients are listed below.

Filler: microcrystalline cellulose

Selection of the microcrystalline cellulose is likely to be important for tablet stability over the course of its shelf life. Because almost nine times the amount of microcrystalline cellulose is used compared to misoprostol 1% HPMC dispersion, the water content of this excipient will contribute most to the overall water content of the finished product.

Selected grades of Avicel® microcrystalline cellulose (FMC biopolymer) and their water content are shown below. Other manufacturers of microcrystalline cellulose make products with similar specifications.

Table M-18. Grades of Avicel® Microcrystalline Cellulose and their Water Contents

PRODUCT GRADES	NOMINAL PARTICLE SIZE, µM	MOISTURE %	LOOSE BULK DENSITY G/mL
Avicel PH-102	100	3.0–5.0	0.28–0.33
Avicel PH-103	50	NMT 3.0	0.26–0.31
Avicel PH-113	50	NMT 2.0	0.27–0.34
Avicel PH-112	100	NMT 1.5	0.28–0.34

Two factors determine the selection of the grade of microcrystalline cellulose to use in the production:

- Whether a drying stage is to be incorporated
  - If the microcrystalline cellulose will be dried to a low-moisture specification, then consider a microcrystalline cellulose with particle size that is compatible with dispersion for effective blending, and rheology of bulk and compression results (hardness, friability, low weight variation, etc.). The initial water content of the excipient will influence the drying time, but the rate of moisture absorption after drying should also be taken into account.
  - If no drying stage is incorporated, then a microcrystalline cellulose with the lowest moisture content, such as PH-112 (moisture not more than 1.5%), would seem appropriate to use.

[53] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46th report. WHO Technical Report Series, No. 970. Geneva: WHO.

- Grade required for most efficient blending and tablet pressing
  - Selection of a grade that will result in more effective blending with the API may be critical to ensure content uniformity, rheology properties, and tablet pressing results. This is especially true for misoprostol 200 mcg tablets because the small amount of misoprostol API relative to the microcrystalline cellulose can make uniform blending challenging.

Disintegrant: sodium starch glycolate

This material is used to promote disintegration of the tablet and is recommended for use in tablets prepared by a dry compression process. Sodium starch glycolate is hygroscopic in nature. It swells rapidly when it comes in contact with water, resulting in rapid disintegration and dissolution. The European and US Pharmacopeias differentiate the properties of sodium starch glycolate types A, B and C as summarized below.

Table M-19. Properties of Sodium Starch Glycolate

TEST	TYPE A	TYPE B	TYPE C
pH	5.5–7.5	3.0–5.0	5.5–7.5
NaCl	Max 7%	Max 7%	Max 1%
LOD	Max 10%	Max 10%	Max 7%
Assay Na	2.8–4.2%	2.0–3.4%	2.8–5.0%

Sodium starch glycolate type A with low moisture content should be used in the manufacture of misoprostol tablets.

Manufacturing process

Environmental conditions and moisture exclusion

Environmental conditions during all stages of production, from weighing, blending, compression, and blistering should be carefully controlled to exclude moisture. Since misoprostol tablets are manufactured as a typical dry blend, much can be prepared in an 8-hour shift, from weighing of starting materials to cold aluminum formed blister packing.

Closed and continuous production systems are preferred to open and discontinuous processes.

The selection of the environmental temperature and relative humidity conditions may depend on the length of each of the stages of production, the time between stages, and how blended materials or bulk tablets are packed and stored.

If specific stages of production such as compression or blistering are expected to take more than several hours, consideration should be given to reducing the relative humidity for the stages to reduce overall exposure to moisture. Alternatively, storage of amounts of material needed for less than one hour of operations in sealed containers containing a desiccant should be considered. The use of desiccant should be studied carefully because in high–relative humidity conditions and/or prolonged storage it might create a microenvironment of high moisture and increase the risk of transfer of moisture to the bulk.

If desiccant is used to protect the bulk product, manufacturers should use airtight containers (aluminum, stainless steel, or other suitable canister) and replace the desiccant bags every time the canister is opened, or with frequency, to prevent moisture transfer. Desiccant bags should be dedicated and regenerated to prevent cross-contamination with other chemicals.

Good practice: suggested conditions for production are as follows:

- Temperature: not more than 25°C.
- Relative humidity: 30–50% depending on the length of time bulk blend or tablets are exposed to the atmosphere.
- Manufacturers should validate their production processes at the temperature and humidity levels selected for manufacture.

In-process controls

In a typical 200-mcg misoprostol tablet, 20 mg of the misoprostol 1% dispersion in HPMC is mixed with 180 mg of excipients. However, the actual content of misoprostol in the final product (200 mcg), is 0.1% the weight of a 200-mg tablet. The very low ratio of pure drug substance to the excipients can present a challenge to uniform blending, which will be critical to ensure good uniformity of content of finished product.

A validated blending process is critical, but sampling of the final blend from multiple locations in the bulk blend should be conducted for every batch to ensure the consistency of the blending process.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Hold times in production

Short holding times between stages of production reduce potential exposure to moisture. Validation of holding times longer than 8 hours should be studied with caution, because one of the critical factors is the acceptance criteria. The main objective of this manual is to reduce variability within a batch and among batches, and to aim for the most stringent limits to assure not only homogeneity within a batch and among batches but also to improve the shelf life of the finished product.

Good practice: All production processes from blending to blistering should be carried out in as short a time as possible to reduce the possibility of exposure to moisture during production.

Storage conditions during production

The best practice is to blend, tablet-press, and foil-pack misoprostol tablets in a single day's operation. Where this is not possible, amounts of material required for a one-hour operation should be packed in virgin bags with the best possible barrier to moisture. If thermo-sealing is not possible, plastic ties can be used. Double bagging is better than single bags and a sturdy secondary container (plastic or stainless steel drum) with tight sealing and light protection is preferred.

The inclusion of a desiccant for storage is recommended, but the use of desiccants between bags or inside the drums should be studied with care to avoid possible release of moisture from desiccant to bulk or tablets.

Packaging

Misoprostol tablets in certain low- and middle-income countries are likely to be subjected to conditions of high humidity and temperature. Packaging that reduces water vapor transmission should ensure stability of the medicine during its shelf life. At 38°C and 90% relative humidity, cold-form aluminum completely prevents water vapor transmission. PVC, by contrast, has much higher water vapor transmission rate (2.4–4 g/m^2/day) under these conditions, which may occasionally be experienced during storage in hot and humid countries. Different grades of PVC/PVDC are also more protective than PVC, but not as protective as aluminum. The table below shows water vapor transmission rates (WVTR) for selected packaging.

Table M-20. Comparative Moisture Barrier Properties of Blister Packaging Materials

TYPICAL WVTR G/M^2/DAY 38°C/90%RH	
Cold-form aluminum	0.00
PVC/80g PVDC	0.31
PVG/60g PVDC	0.47–0.6
PVC/40g PVDC	0.7–0.75
PVC	2.4 –4.0

Good practice: Misoprostol tablets should be packed in an aluminum-aluminum blister pack to reduce the risk of exposure to moisture in humid environments.

Suitability of the aluminum foil should be demonstrated, including:

- Safety: declarations as to compliance with appropriate food additive regulations (e.g., USFDA or EU regulations)
- Protection: WVTR and light transmission (LT) rate as per USP<671>
- Compatibility: accelerated and long-term stability data for the packaged finished products

Bioequivalence requirements

A randomized, single-blind, single-dose, two-treatment, two-period, crossover bioequivalence study in healthy adult female subjects under fasting conditions is required. An appropriate comparator product is Cytotec® (misoprostol 200 mcg tablet, Searle/Pfizer), purchased from an SRA market.

Misoprostol has a range of therapeutic indications, employing a variety of routes of administration. However, it should be noted that the bioequivalence between the proposed and comparator products demonstrated following oral administration cannot be extrapolated to the other routes of administration. To obtain the full range of indications and routes of administration for a misoprostol product, in addition to the bioequivalence study employing oral administration as described above, the following data are required:

- Data from a single-dose, crossover bioequivalence study employing sublingual administration. Proof of bioequivalence in this study would be considered sufficient information to grant indications employing sublingual and buccal routes of administration.
- Pharmacokinetic data (not necessarily a bioequivalence study) showing that, following vaginal administration, the proposed product produces in vivo misoprostol concentrations with a mean maximal concentration (Cmax) of at least 200 pg/mL (normalized for an 800-mcg dose) and an extent of absorption (area under the curve [AUC]) that exceeds that observed following oral administration of the product (on a dose-normalized basis).
- Further, additional dissolution data will be needed to accept the product for the indication of "induction of labor" due to the required administration of fractional doses.

HEAT-STABLE CARBETOCIN

INJECTION, 100 MICROGRAMS/ML

GENERAL PRODUCT INFORMATION

Postpartum hemorrhage (PPH) is commonly defined as a blood loss of 500 mL or more within 24 hours after birth. PPH is the leading cause of maternal mortality in low- and middle-income countries (LMICs) and the primary cause of nearly one quarter of all maternal deaths globally. The majority of deaths due to PPH could be avoided through the use of prophylactic uterotonics during the third stage of labor and by timely and appropriate management.

Carbetocin is a long-acting synthetic agonist analogue of human oxytocin. It has a greater biological effect and longer half-life than oxytocin.54 It has been used for the prevention of PPH following Caesarean section births since 1997. The original formulation requires refrigeration.[55]

Recently, a heat-stable formulation of carbetocin was developed to specifically address limitations in refrigeration and cold-chain transport of PPH medications in LMICs. The heat-stable formulation, consisting of 0.1 micrograms/mL carbetocin in sodium succinate buffer, mannitol, and methionine, is stable at temperatures up to 30°C.[56] When used for PPH prevention after vaginal birth, heat-stable carbetocin has demonstrated non-inferiority to oxytocin for the prevention of blood loss of at least 500 mL or the use of additional uterotonic agents.[57]

Heat-stable carbetocin is included on the WHO Model List of Essential Medicines (EML), and in the WHO recommendations on uterotonics for the prevention of postpartum hemorrhage.[58] WHO recommends the use of heat-stable carbetocin (100 micrograms/mL, intramuscularly or intravenously), along with misoprostol and ergometrine, for the prevention of PPH for all births in settings where oxytocin is

---

[54] Dell-Kuster, S., Hoesli, I., Lapaire, O. et al. 2016. "Efficacy and safety of carbetocin applied as an intravenous bolus compared to as a short-infusion for caesarean section: study protocol for a randomized controlled trial." Trials 17: 155. https://doi.org/10.1186/s13063-016-1285-5.

[55] Widmer, M., Piaggio, G., Abdel-Aleem, H. et al. 2016. "Room temperature stable carbetocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally: study protocol for a randomized controlled trial." Trials 17: 143. https://doi.org/10.1186/s13063-016-1271-y

[56] Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." J Pept Sci 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

[57] Widmer, M., Piaggio, G., Nguyen, T.M., et al. 2018. "Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth." New England Journal of Medicine 379(8): 743-752. doi: 10.1056/NEJMoa1805489

[58] WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1 Last accessed: August 2022

unavailable or its quality cannot be guaranteed, and where its cost is comparable to other effective uterotonics.

It should be noted that the WHO recommendation applies only to the use of carbetocin for the prevention of PPH. Unlike oxytocin, misoprostol and ergometrine, carbetocin is not indicated for treatment of PPH, and it is contraindicated during pregnancy and must not be used for the induction or augmentation of labor.

Heat-stable carbetocin is available under the proprietary names Pabal®, Duratocin®, and Carbetocin Ferring. When cost is a concern, it should be noted that Carbetocin Ferring is made available by Ferring at an affordable and sustainable price for use in public-sector healthcare facilities in LMICs. This price is a subsidized price of $0.31 ± 10% per ampoule of 100 micrograms Carbetocin Ferring, Ex Works.[59] This is comparable to the current United Nations Population Fund (UNFPA) price for oxytocin of $0.33 per unit (10 I.U.), making Carbetocin Ferring a cost-effective option in low-income settings.

KEY CONSIDERATIONS IN PROCUREMENT

4. Only the heat-stable formulation of carbetocin should be procured. Procurers should pay attention to the formulation declared by the manufacturer and product labeling for storage at room temperature (below 30°C).

5. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

6. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use, as carbetocin is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product formulation

The heat-stable formulation differs from the non-heat-stable (refrigerated) formulation only in its excipients. Comparison of the two existing formulations of carbetocin is shown in Table C-1 below.

[59] Ferring Pharmaceuticals. 2020. "Swissmedic approves Carbetocin Ferring for the prevention of postpartum haemorrhage in all births." Available at: https://www.ferring.com/swissmedic-approves-carbetocin-ferring-for-the-prevention-of-postpartum-haemorrhage-in-all-births/ Last accessed: August 202

Table C-1. Composition of heat-stable carbetocin injection60

CARBETOCIN HEAT-STABLE FORMULATION		CARBETOCIN REFRIGERATED FORMULATION	
Component	**Function**	**Component**	**Function**
Carbetocin	Active ingredient	Carbetocin	Active ingredient
Succinic acid	Buffer	Sodium chloride	Isotonicity agent
Mannitol	Isotonicity agent	Glacial acetic acid	pH adjustment
L-methionine	Antioxidant	Water for injection	Solvent
Sodium hydroxide	pH adjustment		
Water for injection	Solvent		

Procurement of carbetocin heat-stable formulation as per the WHO EML is recommended.

Product specification

Heat-stable carbetocin injection products must comply with the quality specifications suggested in "Product Specifications" section below.

Packaging and labeling

Heat-stable carbetocin injection is supplied in single-dose ampoules (e.g. Carbetocin Ferring) and single-dose vials (e.g. Pabal®, Duratocin®) containing 100 micrograms in 1 mL.
The container-closure system (ampoule/vial) must be sufficient to preserve sterility during the shelf life of the product. Additional information about heat-stable carbetocin injection packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Heat-stable carbetocin does not need to be maintained in the cold chain, but should be stored below 30°C. Procurers must ensure that the product is stored safely so that the ampoule/vial cannot break or leak, which would compromise its sterility.

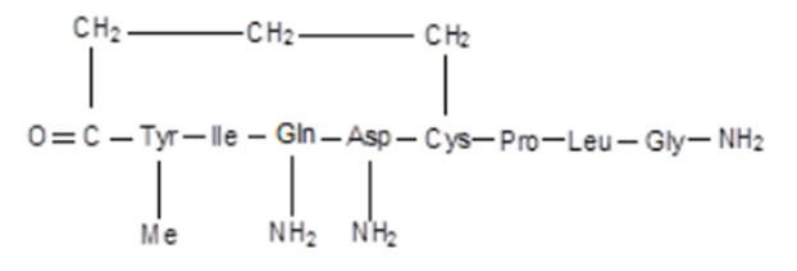
Name of the Medicinal Product	Heat-stable carbetocin injection
Chemical Name	Carbetocin 1-desamino-1-monocarba-2-(0-methyl)-tyrosine oxytocin

60 Widmer, M., Piaggio, G., Abdel-Aleem, H. et al. 2016. "Room temperature stable carbetocin for the prevention of postpartum hemorrhage during the third stage of labor in women delivering vaginally: study protocol for a randomized controlled trial." Trials 17: 143. https://doi.org/10.1186/s13063-016-1271-y

Carbetocin is a long-acting synthetic agonist analogue of human oxytocin, with antihemorrhagic and uterotonic activities. Upon administration, carbetocin binds to oxytocin receptors in the uterine smooth muscle, resulting in rhythmic contractions, increased frequency of existing contractions, and increased uterine tone.

Chemical Structure

$C_{45}H_{69}N_{11}O_{12}S$



Qualitative and Quantitative Composition

Sterile solution for injection
A clear, colorless solution
Heat-stable carbetocin injection contains 100 micrograms of carbetocin per mL.

List of typical excipients[61]:

- L-methionine
- Succinic acid
- Mannitol
- Sodium hydroxide for pH adjustment
- Water for injection

Packaging and Presentation

The WHO EML states "carbetocin injection (heat stable) 100 micrograms/mL", which does not preclude procurement of any particular presentation of carbetocin. Heat-stable carbetocin injection is packed in glass ampoules or vials.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

61 Based on the formulation of an innovator product, Duratocin® / Pabal®.

WHO-prequalified products

As of August 2022, there is only one heat-stable carbetocin injection product prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

Table C-2. List of WHO-prequalified heat-stable carbetocin injection

WHO REF. NUMBER	RH095
MARKETING AUTHORIZATION HOLDER	Ferring International Center SA, Chemin de la Vergognausaz 50, St Prex, 1162, Switzerland
MANUFACTURING SITE	FPP manufacturing site: - Ferring Pharmaceuticals (China) Co Ltd, No. 6 HuiLing Lu (Ferring Road), National Health Technology Park, Zhongshan City, Guangdong Province, China (People's Republic of) - Steril-Gene Life Sciences (P) Ltd., 45, Mangalam Main Road, Mangalam Village, Villianur Commune, Puducherry, 605 110, India API manufacturing site: PolyPeptide Laboratories France SAS, Buildings 1 and 2, 7 rue de Boulogne, Strasbourg, 67100, France
DOSAGE FORM AND STRENGTH	Solution for injection 100 micrograms/mL
PACKAGING AND PRESENTATION	Ampoule; Type I glass 1 mL x 10's
DATE OF PRE-QUALIFICATION	July 4, 2022
SHELF LIFE	48 months
STORAGE CONDITION	Do not store above 30°C. Do not freeze. Keep ampoules in the outer carton, in order to protect from light.

Heat-stable carbetocin

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
PABAL 100 micrograms/mL solution for injection	UK MHRA	Ferring Pharmaceuticals Ltd, UK	PL 03194/0058	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	Keep vials in the outer carton, in order to protect from light. Store below 30°C. Do not freeze.
Carbetocin Ferring Injektionslösung 100 µg/mL	Swissmedic (Switzerland)	Ferring AG, Switzerland	67157	Type I glass ampoule	Not specified	Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.
PABAL Injektionslösung 100 µg/ml	Swissmedic (Switzerland)	Ferring AG, Switzerland	58079	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	Not specified	Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.
PABAL 100 microgrammes/mL, solution injectable	ANSM, France	Ferring SAS, France	34009 550 109 2 0	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	Store the vials in the original outer packaging, in order to protect from light. Store at a temperature not exceeding 30°C. Do not freeze.
PABAL 100 Mikrogramm/mL Injektionslösung	BfArM, Germany	Ferring Arzneimittel GmbH, Germany	64579.00.00	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	The vials should be kept in the original packaging in order to protect the contents from light. Do not store above 30°C. Do not freeze.
Pabal 100 mikrogram/mL injektionsvätska, lösning	MPA, Sweden	Ferring Läkemedel AB, Sweden	24549	Type I glass vials (2R) with type 1 bromobutyl stoppers with aluminum crimp cap	3 years	Store the vials in the outer carton. Sensitive to light. Do not store above 30°C. Do not freeze.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
DURATOCIN solution for injection, 100 micrograms/mL	Health Canada	Ferring INC, Canada	02496526	Colorless glass vials with bromobutyl rubber stoppers and aluminum crimp cap.	Not specified	Store at room temperature (15°C to 30°C).
DURATOCIN 100 micrograms/mL solution for injection	TGA Australia	Ferring Pharmaceuticals Pty Ltd, Australia	AUST R 233671	1 mL clear glass vial with a bromobutyl rubber stopper and an aluminum crimp cap with a tear-off over cap	3 years	Store below 30°C. Once the vial has been opened, the product should be used immediately.

SRA-approved products

Table C-3. Examples of SRA-approved heat-stable carbetocin injection

Note: Carbetocin is not available in the United States.

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedicinfo.ch/
- HealthCanada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other presentations of carbetocin injection that exist in the market include:

- Carbetocin 100 micrograms/mL solution for injection in pre-filled glass syringe

It is used for the same indications, dosage and administration. However, it should be noted that carbetocin injection in pre-filled syringe is the non-heat-stable formulation, which contains sodium chloride, acetic acid for pH adjustment, and water for injections. It is typically labeled for storage under refrigerated conditions, between 2–8°C.62

STORAGE, STABILITY, AND DEGRADATION

Shelf life: 36–48 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.

62 Medicines & Healthcare Products Regulatory Agency (MHRA). 2021. Summary of Product Characteristics of Carbetocin 100 micrograms/mL solution for injection in pre-filled syringe. Available at: https://mhraproducts4853.blob.core.windows.net/docs/a64a13c549a55f490a0b84f6db5be369b52c5a14 Last accessed: August 2022

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table C-2 and Table C-3 above respectively.
Malm et al.[63] reported that the main degradation routes of carbetocin are found to be deamidation, oxidation, and racemization. Deamidation of the amide side-chains of asparagine and glutamine and the amidated glycine C-terminus is favored by low pH (acid-catalyzed hydrolysis), and to some extent by high pH (direct base hydrolysis). The thioether linkage is sensitive to oxidation, which is accelerated by increasing pH. The racemization of the asparagine residue from the L to the D-form is an important degradation route at pH-values above ≈ 6. Due to the presence of an antioxidant (methionine) in the heat-stable carbetocin formulation, degradation by oxidation was negligible at all pH-values. The optimum pH where the sum of remaining degradation pathways is minimized was determined to be pH 5.45.

PRODUCT SPECIFICATIONS

There is currently no published pharmacopeial specifications for heat-stable carbetocin 100 micrograms/mL injection. Therefore, the product should meet the in-house specifications established by the manufacturers, which should comply with the ICH Q6A guideline.[64] Some general factors that the procurers should consider when assessing the in-house specifications of heat-stable carbetocin injection are highlighted in this section. Additional considerations in quality assessment of heat-stable carbetocin are included in part 2 of the attached Annex.

The minimum parameters to be included in the product specifications of heat-stable carbetocin injection include appearance, pH, identification and assay of active pharmaceutical ingredient (API), impurities, identification and assay of methionine (antioxidant), bacterial endotoxins, sterility, extractable volume and particulate matter.

Due to the lack of compendial methods, any in-house analytical procedures (e.g. HPLC assay and impurity methods) used for routine testing of heat-stable carbetocin injection should be shown to be fully validated.

pH

The study from Malm et al. demonstrated the optimum pH of heat-stable carbetocin to control the amount of impurities as pH 5.45. Heat-stable carbetocin injection can therefore be expected to demonstrate a pH in the region of that value for optimum stability.

---

[63] Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." J Pept Sci 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

[64] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1999. "Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A." Geneva: ICH. Available at: https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf

Assay of API (carbetocin)

The acceptable limit for the API content in the product release specifications is ± 5% of the label claim (i.e. 95.0–105.0%), whereas it is ± 10% of the label claim (i.e. 90.0–110.0%) in the shelf-life specifications.

Impurities

According to the study from Malm et al., known degradation products found in heat-stable carbetocin injection are shown in the below table:

Table C-4. Degradation products of carbetocin

MATERIAL	PATHWAY
[Gly9-OH]carbetocin	Hydrolysis
[Asp5]carbetocin	Hydrolysis
[βAsp5]carbetocin	Hydrolysis
[Glu4]carbetocin	Hydrolysis
Carbetocin sulfoxide isomer 1	Oxidation
Carbetocin sulfoxide isomer 2	Oxidation
[D-Asn5]carbetocin	Racemization

Tests and acceptance limits for those impurities as well as the total impurities should be included in the product specifications.
As carbetocin is a synthetic peptide that is beyond the scope of the ICH Q3B guideline[65], the impurities limits should be set based on thresholds for reporting, identification and qualification of organic impurities described in the European Pharmacopeia (Ph. Eur.) General Monograph 'Substances for Pharmaceutical Use' as follows:

- reporting threshold above 0.10%
- identification threshold above 0.5%
- qualification threshold above 1.0%.

Therefore, any impurities observed above the identification threshold (0.5%) should be identified, and the limits above the qualification threshold (1.0%) should be qualified. A limit of no more than 0.5% for unspecified impurities should be included in the heat-stable carbetocin product specifications. Procurers need to verify from manufacturers that there is satisfactory data to justify the impurities limits.

Identification and assay of methionine

L-methionine is included in the heat-stable formulation of carbetocin as an antioxidant. Identification and content determination tests and limits for methionine should therefore be included in the product specifications, according to the Committee for Medicinal Products for Human Use (CHMP) 'Guideline

[65] ICH. 2006. "Impurities in new drug products Q3B(R2)." Geneva: ICH. Available at: https://database.ich.org/sites/default/files/Q3B%28R2%29%20Guideline.pdf

on excipients in the dossier for application for marketing authorisation of a medicinal product'.[66] If the lower limit for the proposed acceptance criterion for the assay of methionine is below 90%, the adequacy of the specified limits should be justified on the basis of controlled conditions and stability testing, to ensure that sufficient antioxidant remains to protect the product throughout its entire shelf-life.

Tests required for parenteral product

Heat-stable carbetocin injection is a parenteral product, it should therefore meet pharmacopeial standards for sterility, bacterial endotoxins, and particulate matter as well.

CARBETOCIN ANNEX

[66] Committee for Medicinal Products for Human Use (CHMP). 2007. "Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product." European Medicines Agency, Amsterdam. (EMEA/CHMP/QWP/396951/2006). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-excipients-dossier-application-marketing-authorisation-medicinal-product-revision-2_en.pdf

PART 1: CLINICAL PARTICULARS[1]

Therapeutic indications

Prevention of postpartum hemorrhage due to uterine atony.

Posology, method, and duration of administration

Posology

Carbetocin must be administered as soon as possible after delivery of the infant and preferably before delivery of the placenta. It should be administered in an obstetric unit by appropriately skilled and trained health care providers

Caesarean section under epidural or spinal anesthesia:

A single dose of 100 micrograms carbetocin (1 mL) by slow intravenous injection (over 1 minute) after delivery of the infant.

There are limited data on the use of carbetocin with general anesthesia.

Vaginal delivery:

A single dose of 100 micrograms (1 mL) by slow intravenous injection (over 1 minute) or by intramuscular injection, after delivery of the infant.

Children and adolescents

Only limited data are available on the safety and efficacy of carbetocin in adolescents after the menarche. In adolescents from the age of 15 years, the same dose as in adults may be administered under adequate supervision, if indicated.

Carbetocin is not recommended in adolescents under 15 years of age, i.e. those who are not yet fully mature, due to lack of data.

There is no indication for use in pre-pubescent children.

Elderly

There is no indication for use in post-menopausal women.

Hepatic or renal impairment

The pharmacokinetics of carbetocin in patients with hepatic or renal impairment have not been investigated. Therefore, carbetocin should not be used in these patients (see "Contraindications" section)

Method of administration

For intravenous or intramuscular administration.
For intravenous administration carbetocin must be administered slowly, over 1 minute.
Carbetocin is for single administration only. No further doses of carbetocin should be administered.

---

1 Based on Carbetocin Ferring Summary of Product Characteristics published by WHO Prequalification (WHO reference number RH095) Available at: https://extranet.who.int/pqweb/sites/default/files/RH095part4v1.pdf Last accessed: March 2023

Contraindications

Carbetocin is contraindicated in the following circumstances:

- Pregnancy and labor before delivery of the infant
- For induction or augmentation of labor
- Serious cardiovascular disorders
- Epilepsy
- Renal or hepatic disorders
- Hypersensitivity to carbetocin, oxytocin or to any of the excipients in the product

Special warnings and precautions for use

Carbetocin should be used only in obstetric units by appropriately skilled and trained health care providers.

Persistent or excessive bleeding

If uterine bleeding persists, the cause must be determined. Possible causes are retained placental fragments, injuries to the perineum, vagina or cervix, inadequate emptying or repair of the uterus after caesarean section, or disorders of blood coagulation.

If uterine hypotonia or atonia persists after administration of carbetocin, with consequent excessive bleeding, therapy with another uterotonic can be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persisting uterine atony after oxytocin administration.

Water retention
Animal studies show that carbetocin has some antidiuretic activity (vasopressin activity: <0.025 IU/vial) and there is, therefore, a risk of water intoxication with hyponatremia, especially in patients receiving large volumes of infusion solutions. Attention should be paid to the early signs of water intoxication or hyponatremia – such as drowsiness, listlessness and headache – to prevent complications such as convulsions and coma.

In the presence of migraine, asthma, cardiovascular disease, and other conditions in which a rapid increase in extracellular water may be hazardous for an already overburdened system, carbetocin should only be used after carefully weighing up of the benefits and risks and under appropriate supervision.

Cardiac risks (including QT prolongation)
Adverse cardiac effects such as bradycardia, QT prolongation, arrhythmias, and myocardial ischemia have occurred with oxytocin, especially after rapid intravenous injection. It is not known if these effects are caused by oxytocin treatment or were caused by other simultaneously administered medicines. There are no data on a possible pathophysiological mechanism. Because carbetocin is structurally closely related to oxytocin, carbetocin should be used with special caution in patients with long-QT syndrome or other risk factors for QT prolongation (such as co-medication with drugs with a risk of QT-prolongation).

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100-microgram ampoule, that is to say it is essentially ‘sodium-free’.

Further precautions
Carbetocin has not been investigated in patients with eclampsia. It should therefore be used with special caution in cases of eclampsia or pre-eclampsia, and patients should be carefully monitored.

Only limited data are available on the use of carbetocin in patients with (gestational) diabetes.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been undertaken with carbetocin.
There is a risk of a cumulative effect with the use of methylergometrine or oxytocin after the administration of carbetocin.

During clinical trials, carbetocin has been administered in association with a number of analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anesthesia. No drug interactions were observed.

The following interactions have occurred involving oxytocin. Since carbetocin is structurally related to oxytocin, they might also occur with carbetocin:

- ■ Prostaglandins potentiate the effect of oxytocin. Therefore, prostaglandins should not be used at the same time as carbetocin. If simultaneous use cannot be avoided, then the patient must be closely monitored.
- ■ Inhalation anesthetics, e.g. halothane, can potentiate the hypotensive effect and reduce the effect of carbetocin on the uterus. In case of concomitant use of such anesthetics with oxytocin, arrhythmias have also been reported
- ■ Hypertension has been reported when oxytocin was given 3 to 4 hours after a vasoconstrictor was administered in conjunction with caudal-block anesthesia.
- Carbetocin can potentiate the hypertensive effect of ergot-alkaloids such as methylergometrine.

Fertility, pregnancy and lactation

Pregnancy

Carbetocin is contraindicated during pregnancy and must not be used for the induction of labor (see "Contraindications" section above).

Breastfeeding

No relevant effects on milk let-down have been reported during clinical trials. Small amounts of carbetocin have been detected in breast milk of nursing women. The small amounts of carbetocin transferred into colostrum or breast milk after a single injection of carbetocin, and subsequently ingested by the infant, are likely to be degraded by enzymes in the gastrointestinal tract and therefore have probably no clinically relevant effects in the breastfed infant.
Breast-feeding can be started without restrictions after the use of carbetocin.

Effects on ability to drive and use machines

No studies of the effect on the ability to respond, to drive and to use machines have been conducted. However, carbetocin can have undesirable effects such as dizziness that could impair the ability to drive.

Undesirable effects

The following statements are based on clinical trials in which carbetocin was used in the context of a Caesarean section. However, a similar safety profile is to be expected on use after vaginal delivery. The undesirable effects observed with carbetocin during the clinical trials after vaginal delivery were also comparable in frequency and severity to those of oxytocin.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as very common (at least 1 in 10); common (1 in 100 to 1 in 10); uncommon (1 in 1000 to 1 in 100); rare (1 in 10,000 to 1 in 1000); or very rare (less than 1 in 10,000).

Table C-5. Adverse events observed with carbetocin

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Blood and lymphatic system disorders	Common: anemia
Immune system disorders	Not known: hypersensitivity reactions (including anaphylactic reactions)
Nervous system disorders	Very common: headache, tremor Common: dizziness
Cardiac disorders	Uncommon: tachycardia (see also "Special warnings and precautions for use" section above)
Vascular disorders	Very common: hypotension, flushing
Respiratory, thoracic, and mediastinal disorders	Common: dyspnea
Gastrointestinal disorders	Very common: nausea, abdominal pain Common: metallic taste, vomiting
Skin and subcutaneous tissue disorders	Very common: pruritus
Musculoskeletal and connective tissue disorders	Common: back pain
General disorders and administration site conditions	Very common: feeling of warmth Common: chills, pain, chest pain, sweating

Reactions at the administration site were not specifically investigated. As with other drugs, local irritation is likely, especially with intramuscular administration.

Overdose

An overdose with uterotonic agents such as carbetocin can induce uterine hyperactivity. Symptoms of an overdose observed with oxytocin are also likely with carbetocin. If carbetocin is used before delivery of the infant (see "Contraindications" section),hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions can occur, with the risk of uterine rupture or increased postpartum hemorrhage.

An overdose may lead to hyponatremia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake.

Treatment of overdosage consists of symptomatic and supportive therapy. If signs or symptoms of overdosage occur, oxygen should be given. In the case of water intoxication, it is important to restrict fluid intake, initiate diuresis, correct electrolyte disturbances, and control convulsions if they occur.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of heat-stable carbetocin products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on heat-stable carbetocin injection.

API

As of August 2022, there is no carbetocin API prequalified by the WHO PQP. Certificate of suitability to monographs of the European Pharmacopeia (CEP) is not applicable since no Ph. Eur. monograph exists for carbetocin.

The WHO-prequalified heat-stable carbetocin injection (Carbetocin Ferring) has used carbetocin API manufactured by PolyPeptide Laboratories France SAS.2 This manufacturer can be considered as a trusted source as it has passed the assessment of WHO PQP team. However, it is recommended to check for updated information on the WHO PQP website at the time of quality assessment. Other manufacturers of carbetocin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines[3] to support the quality assessment.

There is currently no published pharmacopeial specifications for carbetocin API. Therefore, in-house specifications should be established by the manufacturers and adhere to the ICH Q6A guideline. The typical specifications of carbetocin API include the following parameters: identification, assay, related substances, specific optical rotation, water content, acetic acid content, residual solvents, microbial limits, and bacterial endotoxins.[4] If intended for use in the aseptic manufacture of heat-stable carbetocin injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

According to Malm et al.,5 [D-Cys6]carbetocin and [des-Gln4]carbetocin are known synthesis-related impurities of carbetocin API. They should therefore be appropriately controlled in the specifications of carbetocin API. Furthermore, any impurities above the identification threshold given in the Ph. Eur. General monograph 'Substances for pharmaceutical use' (0.5%) should be identified, and the limits above the qualification threshold (1.0%) should be qualified. A limit of not more than 0.5% for unspecified impurities should be included in the carbetocin API specifications.

2 WHO. 2022. Prequalified medicinal products: RH095. Available at: https://extranet.who.int/pqweb/medicine/4419 Last accessed: August 2022

3 WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.

4 PolyPeptide Group. 2021. Carbetocin drug substance specification. Available at: https://www.polypeptide.com/wp-content/uploads/2018/09/Carbetocin-web-spec-2021.pdf Last accessed: August 2022

5 Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." J Pept Sci 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

Carbetocin is hygroscopic.[6] It should be stored in a tightly closed original container at 2–8°C and avoid exposure to light,[7] or in the conditions recommended by the API manufacturer.

Excipients

The typical excipients of heat-stable carbetocin injection are shown in the table below.8 There are no special concerns with the excipients. No excipient with the risk of transmitting TSE/BSE is used.0
Table C-7. Excipients of heat-stable carbetocin injection

INGREDIENT	FUNCTION
L-methionine	Antioxidant
Succinic acid	Buffer agent
Mannitol	Isotonicity agent
Sodium hydroxide	pH adjustment
Water for injection	Solvent

Excipients should be controlled according to the requirements of the officially recognized compendial standard (Ph.Int., Ph.Eur./BP, USP), and include a test for bioload or bacterial endotoxins.

If excipients not contained in the innovator product are used in any generic products, it is necessary to demonstrate compatibility with the carbetocin API through chromatographic results (assay, purity). The choice of excipients, their concentration and their characteristics can influence the heat-stable carbetocin product performance and therefore should be discussed relative to their respective functions.

Manufacturing process

The manufacturing process of heat-stable carbetocin injection is a standard process—conducted under appropriate aseptic conditions—including the solution preparation steps with adjustment of pH, pre- and sterile filtration, filling and sealing of the ampoules/vials. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

The pH adjustment is crucial for heat-stable carbetocin stability because it was shown by Malm et al.[9] that carbetocin is most stable at pH 5.45 with low degradation (≤ 4%) after 12 months at 40°C/75% RH. Carbetocin was found to degrade mainly by deamidation of the glutamine residue and the amidated glycine C-terminus at pH-values below the optimum and by racemization of the asparagine residue at pH values above the optimum.

The filters used in the sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components.

---

6 https://www.trc-canada.com/product-detail/?C175925 Last accessed: August 2022
7 PolyPeptide Group. 2019. Carbetocin safety data sheet. Available at: https://www.polypeptide.com/wp-content/uploads/2018/09/Carbetocin-SDS-v10-UK.pdf Last accessed: August 2022
8 Based on formulation of an innovator product, , Duratocin® / Pabal®.
9 Malm, M., Madsen, I., Kjellström, J. 2018 "Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries." J Pept Sci 24(6): e3082. doi: 10.1002/psc.3082. Epub 2018 Apr 27. PMID: 29700898; PMCID: PMC6001700.

The selection of the environment temperature conditions may depend on the length of each of the stages of production, the time between stages and how bulk solution is packed and stored.

Nitrogen purging should be carried out throughout the manufacturing and filling process to minimize contact with atmospheric and dissolved oxygen. If bulk solution storage is required, store the solution under a nitrogen blanket. The lid of the manufacturing tank should be opened and closed immediately after each addition.

Heat-stable carbetocin injection may be manufactured by aseptic technique for the whole process. When aseptic processing is used, all the ingredients must be sterile grade and comply with the test for sterility before use.

For the validation of aseptic processing, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

A manufacturing process validation protocol for the validation of the first three production scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. In cases where the manufacturer is already manufacturing production scale batches, full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule or vial should be used.
Suitability of the container should be demonstrated, including the following properties:

Safety

■ Glass ampoule/vial must meet compendial requirements such as USP<660> and USP<1660>.
■ Rubber stopper (for vial) must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
■ Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:

- One-time test reported as part of product development
- Routine leak testing performed as part of product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as sorption.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Pabal® (carbetocin 100 micrograms/mL injection, Ferring) and Duratocin® (carbetocin 100 micrograms/mL injection, Ferring). The composition of the proposed product should be the same as the comparator product.

Equivalence of any generic heat-stable carbetocin products with the comparator product should be demonstrated, and the applicant should provide comparative results of physicochemical properties (e.g. pH, density, osmolarity etc.) for both the generic and comparator products.

MAGNESIUM SULFATE

INJECTION, 500 MG/ML IN 2-ML AND 10-ML AMPOULE

GENERAL PRODUCT INFORMATION

Pre-eclampsia and eclampsia is the second-leading cause of maternal death in low- and middle-income countries. It is most often detected through the elevation of blood pressure during pregnancy, which can be followed by seizures, kidney and liver damage, and maternal and fetal death, if untreated.

Magnesium sulfate is recognized by WHO as the safest, most effective, and lowest-cost medicine for treating severe pre-eclampsia and eclampsia. It is also considered an essential medicine by the UN Commission on Life-Saving Commodities for Women and Children. Other anticonvulsant medicines, such as diazepam and phenytoin, are less effective and riskier. Magnesium sulfate should be the only treatment of severe pre-eclampsia and eclampsia and should be procured over other anticonvulsants and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

Additionally, WHO recommends the use of magnesium sulfate for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of neurological complications (neuroprotection). Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours. Magnesium sulfate should be administered regardless of the cause for preterm birth and the number of babies in utero.[1]

[1] WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. Geneva: World Health Organization; 2015. Available from: http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO or approved by a SRA for magnesium sulfate injection and those with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is sterile and safe for patient use as magnesium sulfate is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Products that are procured must comply with pharmacopeial specifications, such as those of the International Pharmacopoeia, US Pharmacopeia, and British Pharmacopeia, as detailed in the "Supply" section 4 below.

Packaging and labeling

The container-closure system (ampoule) must be sufficient to preserve sterility during the shelf life of the product.

Procurement of 500 mg/mL (50% w/v) in 2-mL and 10-mL ampoule presentations as per the WHO EML is recommended. The WHO EML recommends magnesium sulfate 500 mg/mL (50% w/v) in 2-mL and 10-mL ampoule presentations, for convenient use in both Pritchard (IV/IM) and Zuspan (IV/IV) dosing regimens for the treatment of eclampsia and severe pre-eclampsia. Some SRA-approved products are presented in different packaging and/or concentrations, which require an adaptation of the dilution process during dosage preparation. The additional burden of recalculation is time-consuming and can introduce potential errors.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Magnesium sulfate must be stored safely to ensure that ampoules do not break or leak, which would compromise their sterility. Products do not need to be maintained in the cold chain.

Name of the Medicinal Product	Magnesium sulfate injection
Chemical Name	Magnesium sulfate (1:1) heptahydrate
Chemical Structure	$MgSO_4$, $7H_2O$
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Magnesium sulfate injection is a sterile solution of magnesium sulfate heptahydrate in water for injection. It contains 500 mg of magnesium sulfate heptahydrate per mL (50% w/v), approximately 2 millimoles magnesium ions (Mg^{2+}) per mL 1 ampoule (2 mL) contains 1,000 mg of magnesium sulfate heptahydrate. 1 ampoule (10 mL) contains 5,000 mg of magnesium sulfate heptahydrate. List of typical excipients: – Water for injections – Sulfuric acid/Hydrochloric acid and/or sodium hydroxide, for pH adjustment
Packaging and Presentation	The WHO Essential Medicines List includes two presentations: 500 mg/mL in 2-mL ampoule (equivalent to 1 g in 2 mL; 50% w/v) and 500 mg/mL in 10-mL ampoule (equivalent to 5 g in 10 mL; 50% w/v). These ampoules would need to be mixed with IV solution to dilute to 20 percent solution for an IV loading dose.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from the trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of June 2022, there are seven magnesium sulfate injections prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

Table MS-21. List of WHO-Prequalified Magnesium Sulfate Injection

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH062(a)	Inresa Arzneimittel GmbH, Obere Hardtstraße 18, 79114, Freiburg, Germany	FPP manufacturing site: Laboratoire Renaudin, ZA Errobi, 64250, Itxassou, France API manufacturing site: – K+S KALI GmbH, Bertha-von-Suttner-Strasse 7, Kassel, Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 50%	Ampoule: type I glass 10 mL x 5's 10 mL x 10's 10 mL x 50's 10 mL x 100's	15-Aug-16	3 years	Do not store above 25°C.
RH063	AS Kalcecks, Krustpils iela 71E, Rīga, LV-1057, Latvia	FPP manufacturing site: – HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia – Mefar Ilac Sanayii A.S., Ramazanoglu Mah. Ensar Cad. No: 20, Kurtkoy-Pendik, Istanbul, TR-34906, Turkey API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (2 mL)	Ampoule: type I glass 2 mL x 10's 2 mL x 100's	4-Jul-17	5 years	Do not store above 30°C.
RH064	AS Kalckeks, Krustpils iela 71E, Rīga, LV-1057, Latvia	FPP manufacturing site: – HBM Pharma sro, Sklabinska 30, Martin, 036 80, Slovakia – Mefar Ilac Sanayii A.S., Ramazanoglu Mah. Ensar Cad. No: 20, Kurtkoy-Pendik, Istanbul, TR-34906, Turkey	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass 10 mL x 5's 10 mL x 10's 10 mL x 100's	4-Jul-17	5 years	Do not store above 30°C.

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
		API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic					
RH072(a)	Labesfal, Laboratorios Almiro SA, Unit 2, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal	FPP manufacturing site: Labesfal, Laboratorios Almiro SA, Unit 2, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass, colorless 10 mL x 50's	19-Jun-18	5 years	Do not store above 30°C.
RH073(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 50% w/v, 2 mL	Ampoule; neutral type I glass 2 mL x 10's	12-Dec-17	3 years	Do not store above 30°C.
RH077(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill,	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	Solution for injection 50% w/v, 10 mL	Ampoule; neutral type I glass 10 mL x 10's	12-Dec-17	3 years	Do not store above 30°C.

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
	Romford, Essex, RM3 8UG, United Kingdom	API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic					
RH086	Joint-Stock Company Halychpharm, 6/8, Opryshkivska Str., Lviv, 79024, Ukraine	FPP manufacturing site: Joint-Stock Company Halychpharm, 6/8, Opryshkivska Str., Lviv, 79024, Ukraine API manufacturing site: Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass 10 mL x 5's x 2	16-Mar-20	4 years	Do not store above 30°C. Do not freeze.

(a) *Indicates SRA-approved product that has been prequalified based on abbreviated assessment.*

SRA-approved products

Table MS-22. Examples of SRA-Approved Magnesium Sulfate 500 mg/mL in 2-mL and 10-mL Ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Magnesium sulfate 50% w/v solution for injection or infusion	UK MHRA	Torbay and South Devon NHS Foundation Trust, UK	PL 13079/0004	Glass ampoule: 2 mL, 10 mL	3 years	This medicinal product does not require any special storage conditions.
Magnesium Sulfate 50%w/v Solution for Injection	UK MHRA	Aurum Pharmaceuticals Ltd, UK	PL 12064/0013	Glass ampoule: 2 mL, 10 mL	3 years	Do not store above 25°C.
Magnesium Sulfate 50% w/v Solution for Injection/ Infusion	UK MHRA	AS KALCEKS, Latvia	PL 47015/0010	Glass ampoule: 2 mL, 10 mL	30 months	Do not freeze.
Magnesium sulfate 50% w/v solution for injection	Swissmedic	Grosse Apotheke Dr. G. Bichsel AG, Switzerland	56394	Glass ampoule: 2 mL, 10 mL	Not specified	Store at room temperature (15–25°C).

Note: Magnesium sulfate injection 50% products that are approved by the US FDA (e.g. those supplied by Fresenius Kabi, Hospira Inc, Exela Pharma) are not included in the list above, as they are available in glass vials of 10 mL, 20 mL, and 50 mL different from the presentations as per the WHO recommendation.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedicinfo.ch/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods.

Related products

Other formulations of magnesium sulfate injection on the market include the following products:

Magnesium sulfate 10% w/v	Indicated in adults, adolescents, and children for: i) treatment of magnesium deficiency in proven hypomagnesemia; and ii) prevention and treatment of hypomagnesemia in patients receiving total parenteral nutrition Indicated in parturients for: i) control and prevention of seizures in severe pre-eclampsia; and ii) control and prevention of recurrent seizures in eclampsia.
Magnesium sulfate 20% w/v	Indicated for prevention of further seizures associated with eclampsia, and for treatment of magnesium deficiency in hypomagnesemia where the oral route of administration may be inappropriate.

STORAGE, STABILITY, AND DEGRADATION

Magnesium sulfate is very stable at ambient temperatures and is unlikely to undergo any significant degradation as a result of heat if it is properly manufactured, packaged, sterilized, and sealed.

Shelf life: 3–5 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30˚C. Do not freeze.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table MS-1 and Table MS-2 above respectively.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the International Pharmacopeia, US Pharmacopeia, and British Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopeias are the same, except for the assay and bacterial endotoxin limits.

Table MS-23. International Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Magnesium	Yield the reactions characteristic of magnesium salts	As per IP monograph of magnesium sulfate injection
b) Sulfate	Yields the reactions characteristic of sulfates	2.1 General identification tests
pH	pH of the injection, diluted to contain 50 mg of magnesium sulfate heptahydrate per mL: 5.5–7.0	1.13 pH value
Assay	90.0–110.0%	2.5 Complexometric titrations
Bacterial endotoxins	Less than 0.18 IU of endotoxin per mg magnesium sulfate heptahydrate	3.4 Test for bacterial endotoxins
Sterility	Sterile	3.2 Test for sterility
Extractable volume	Comply	5.6 Extractable volume for parenteral preparations
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table MS-24. US Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Magnesium	Yield the reactions characteristic of magnesium salts	USP<191>
b) Sulfate	Yields the reactions characteristic of sulfates	USP<191>
pH	pH of the injection, diluted to contain 50 mg of magnesium sulfate heptahydrate per mL: 5.5–7.0	USP<791>
Assay	93.0–107.0%	Titration, USP monograph
Bacterial endotoxins	Not more than 0.09 USP endotoxin unit/mg of magnesium sulfate	USP<85>
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table MS-25. British Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Magnesium	Yield the reactions characteristic of magnesium salts	Appendix VI
b) Sulfate	Yields the reactions characteristic of sulfates	Appendix VI
pH	pH of the injection, diluted to contain 5% w/v of magnesium sulfate heptahydrate per mL: 5.5–7.0	Appendix V L
Assay	95.0–105.0%	Titration, BP monograph
Bacterial endotoxins	Comply	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

MAGNESIUM SULFATE ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

- Prevention of eclampsia in women with severe pre-eclampsia
- Treatment of women with eclampsia
- Prevention of cerebral palsy in the infant of women at risk of imminent preterm birth before 32 weeks of gestation)

Posology, method, and duration of administration

Severe pre-eclampsia and eclampsia

The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia. For settings where it is not possible to administer the full magnesium sulfate regimen, the use of a magnesium sulfate loading dose followed by immediate transfer to a higher-level health care facility is recommended.

Note regarding dilution for IV use

*Magnesium sulfate injection **must** be diluted to a ≤20% solution for intravenous use. Diluents commonly used are 5% glucose solution and 0.9% sodium chloride solution. For a 20% solution, dilute 10 mL of magnesium sulfate injection with 15 mL of diluent.*

Intravenous dosing should be done using an infusion pump if available.

From a microbiological point of view, the reconstituted/diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

Pritchard regimen (IV/IM)

Loading dose (IV and IM):

- Give 4 g IV over five minutes (20 mL of the diluted 20% magnesium sulfate solution).
- Follow promptly with 10 g of 50% magnesium sulfate solution: give 5 g (10 mL of the undiluted 50% solution) in each buttock as a deep IM injection with 1 mL of 2% lidocaine in the same syringe.

Ensure aseptic technique when giving magnesium sulfate deep IM injection. Warn the woman that she will have a feeling of warmth when the magnesium sulfate is given.

If convulsions recur after 15 minutes, give 2 g (10 mL of the diluted 20% magnesium sulfate solution intravenously over 5 minutes.

Maintenance dose (intramuscular):

- Give 5 g (10 mL of the undiluted 50% magnesium sulfate solution) with 1 mL of 2% lidocaine in the same syringe by deep IM injection into alternate buttocks every four hours. Continue treatment for 24 hours after birth or the last convulsion, whichever occurs last.

Zuspan regimen (IV/IV)

See note above on how to dilute the product to a 20% solution.

Intravenous administration, using an infusion pump if available:

Loading dose:

- Give 4 g IV over five minutes (20 mL of the diluted 20% magnesium sulfate solution).
- If convulsions recur after 15 minutes, give 2 g (10 mL of the diluted 20% magnesium sulfate solution) IV over 5 minutes.

Maintenance dose (intravenous):

- Give intravenous infusion 1 g (5 mL of the diluted 20% magnesium sulfate solution) per hour. Continue treatment for 24 hours after childbirth or the last convulsion, whichever occurs last.

Although magnesium toxicity is rare, a key component of monitoring women with severe pre-eclampsia and eclampsia is assessing for signs of magnesium toxicity.

Before administration, it is important to ensure that:

- respiratory rate is at least 16 per minute;
- patellar reflexes are present;
- urinary output is at least 30 ml per hour over 4 hours.

If there are signs of toxicity, the next intramuscular dose should be delayed or the intravenous infusion of magnesium sulfate withheld. Signs indicating the need to withhold or delay maintenance dose of magnesium sulfate are:

- respiratory rate below 16 breaths per minute;
- patellar reflexes are absent;
- urinary output falls below 30 ml per hour over preceding 4 hours.

The antidote (calcium gluconate) should be kept ready. In case of respiratory arrest:

- assist ventilation (mask and bag, anaesthesia apparatus, intubation);
- give calcium gluconate 1 g (10 ml of 10% solution) intravenously slowly over 3 minutes, until respiration begins to counteract the effect of magnesium sulfate.

Prevention of cerebral palsy in the infant of women at risk of imminent preterm birth before 32 weeks of gestation

Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours.

Three intravenous dosing regimens have been used for prevention of cerebral palsy. There is insufficient evidence at present to recommend one over the others:

- 4 g (20 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 20 minutes, then 1 g (5 mL of the diluted 20% magnesium sulfate solution) per hour until delivery or for 24 hours, whichever comes first.
- 4 g (20 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 30 minutes, or as a single intravenous bolus.
- 6 g (30 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 20–30 minutes, followed by maintenance infusion of 2 g (10 mL of the diluted 20% magnesium sulfate solution per hour.

When Magnesium sulfate is administered, women should be monitored for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

Use in patients with renal impairment

In patients with mild to moderate renal impairment, dosage should be reduced. For safe use, vigilance is advised for clinical signs of magnesium toxicity (i.e. respiratory rate falling below 16 /min, absent patellar reflexes, urine output below 30 ml per hour in preceding 4 hours). Monitoring of blood magnesium levels may also be helpful.

In patients with severe renal impairment, magnesium sulfate is contraindicated.

Contraindications

- Hypersensitivity to the active substance, its salts or to any of the excipients
- Heart block
- Severe renal impairment

Special warnings and precautions for use

Clinical indicators of a safe regimen include:

- respiratory rate is above 16 breaths per minute;
- patellar reflexes are present;
- urinary output is above 30 ml per hour over preceding four hours.

When magnesium sulfate is used in pregnant women, fetal heart rate should be monitored (see also "Fertility, pregnancy and lactation" section below).

Parenteral magnesium sulfate should be used with caution in patients with myasthenia gravis.

Magnesium sulfate should be administered with extreme caution in patients receiving β-adrenergic agonists, calcium antagonists, CNS depressants, cardiac glycosides and neuromuscular blocking agents (see also "Interaction with other medicinal products and other forms of interaction" section below).

Alcohol abuse increases the excretion of magnesium resulting in decreased magnesium levels.

Parenteral magnesium sulfate administration is contraindicated in patients with severe renal impairment (see also "Contraindications" section above). It should be used with caution in less severe degrees of renal impairment.

Interaction with other medicinal products and other forms of interaction

Extreme caution must be used when β-adrenergic agonists and calcium-channel blocking agents (e.g. nifedipine) are administered concomitantly with magnesium sulfate due to a risk of serious adverse maternal effects (reduced heart rate, contractility, left ventricular systolic pressure and neuromuscular blockade).

When CNS depressants (e.g. barbiturates, opiates, general anaesthetics) are administered concomitantly with magnesium sulfate, dosage of these medicines must be carefully adjusted because of the additive central depressant effect.

Magnesium sulfate should be used with extreme caution in patients taking digoxin, as it may cause serious changes in cardiac conduction, including heart block.

Concomitant use of neuromuscular blocking agents with magnesium sulfate leads to excessive neuromuscular blockade; these medicines should be administered concomitantly only with caution. Patients should be monitored for respiratory depression.

Magnesium sulfate is incompatible with alkali hydroxides (forming insoluble magnesium hydroxide), alkali carbonates (forming insoluble magnesium carbonate) and salicylates. The activities of antibiotics such as streptomycin and tetracycline are inhibited by magnesium ions. Use with diuretics, aminoglycosides (such as gentamycin, tobramycin amphotericin B), and nephrotoxic immunosuppressants (such as ciclosporin) or cytotoxics (such as cisplatin) may increase the risk of adverse effects. It is also advised that magnesium sulfate not be used in conjunction with benzylpenicillin, nafcillin, polymyxin, dobutamine, or procaine (novocaine).

Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established, however, in the medical emergency of a patient having eclampsia, magnesium sulfate can be administered to relieve this condition, which may be life threatening to both mother and baby.

Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored and use within 2 hours of delivery should be avoided.

Magnesium sulfate can cause skeletal adverse effects in the child when administered continuously for more than 5 to 7 days to pregnant women. There are retrospective epidemiological studies and case reports documenting fetal adverse effects including hypocalcaemia, skeletal demineralization, osteopenia and other skeletal adverse effects with maternal administration of magnesium sulfate for more than 5 to 7 days. The clinical significance of the observed effects is unknown.

If prolonged or repeated exposure to magnesium sulfate occurs during pregnancy, monitoring of neonates for abnormal calcium or magnesium levels and skeletal adverse effects should be considered.

Breastfeeding

Magnesium sulfate is excreted in negligible amounts into breast milk, therefore the use of magnesium sulfate is compatible with breast-feeding.

Postpartum use of intravenous magnesium sulfate for longer than 6 hours appears to delay the onset of lactation.

Fertility

No studies and/or data are available on the effects on fertility.

Effects on ability to drive and use machines

No studies have been carried out on the ability to drive and use machines.

Undesirable effects

Adverse events related to treatment are listed below. They reflect published literature data, but reliable information on frequency is not available.

Table MS-26. Adverse Events Related to Treatment with Magnesium Sulfate Injection

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Immune system disorders	Hypersensitivity reactions, flushing
Metabolism and nutrition disorders	Thirst
Nervous system disorders	Double vision
Psychiatric disorders	Drowsiness, confusion, slurred speech
Cardiac disorders	ECG changes (prolonged PR, QRS and QT intervals), bradycardia, cardiac arrhythmias, cardiac arrest and coma
Vascular disorders	Hypotension
Gastrointestinal disorders	Nausea, vomiting
Respiratory, thoracic, and mediastinal disorders	Respiratory depression*
Musculoskeletal and connective tissue disorders	Loss of tendon reflexes due to neuromuscular blockade, muscle weakness
General disorders and administration site conditions	Pain with intramuscular injection
Investigations	Electrolyte/fluid abnormalities (hypophosphatemia, hyperosmolar dehydration), hypocalcaemia

** There is a risk of respiratory depression when magnesium sulfate is administered concomitantly with high doses of barbiturates, opioids or hypnotics (see also "Interaction with other medicinal products and other forms of interaction" section above).*

Overdose

Symptoms of intoxication

Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. Excessive parenteral doses of magnesium salts lead to the development of hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade.

Other symptoms and signs of hypermagnesaemia may include nausea, vomiting, flushing, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision, muscle weakness, low heart rate, cardiac arrhythmias, electrolyte/fluid abnormalities. In severe cases coma and cardiac arrest may occur.

Patients with renal failure and metabolic derangements develop toxicity at lower doses.

Treatment of intoxication

Assisted ventilation.

Calcium gluconate 1 g (10 mL of 10% solution) given intravenously slowly over 3 minutes, until respiration begins to counteract the effect of magnesium sulfate.

Dialysis may be necessary in patients with renal impairment or severe hypermagnesemia.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of magnesium sulfate injection products. When assessing the complete quality/CMC documentation, assessors should consider the following information on magnesium sulfate injection.

API

As of June 2022, no magnesium sulfate API is prequalified by the WHO PQP.

There are two manufacturers of magnesium sulfate API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal products.

Table MS-27. Manufacturers of Magnesium Sulfate API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Magnesium sulfate heptahydrate (monograph number 44)	Macco Organiques, SRO CZ 792 01 Bruntál, Czech Republic	R0-CEP 2016-148-Rev 00	10/20/2017	Chemistry
Magnesium sulfate heptahydrate (monograph number 44)	PQ CORPORATION, Malvern, USA	R0-CEP 2018-109-Rev 00	6/17/2020	Chemistry

Other manufacturers of magnesium sulfate API should provide evidence for GMP compliance. However, magnesium sulfate is an atypical API; the manufacturing process and controls are not typically designed to meet API GMP. As an alternative, there should be a clear specification, the site should have been audited, changes should be controlled, and appropriate checks should be made on incoming goods.

The specifications of magnesium sulfate API should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP) with additional tests/limits for arsenic if not included in that monograph, as well as tests/limits for bacterial endotoxins. Such additional tests may be based on another pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

Excipients

The excipients of magnesium sulfate injection include water for injection and sulfuric acid/hydrochloric acid and/or sodium hydroxide for pH adjustment. There are no special concerns on the excipients. No excipient with the risk of transmitting TSE/BSE is used.

Manufacturing process

Magnesium sulfate injection is a straightforward product to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.

The manufacturing process of magnesium sulfate injection is a standard process—conducted under appropriate aseptic conditions, including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, and filling and sealing of the ampoules. Finally, steam sterilization by autoclaving of the filled ampoules is performed. The headspace of the ampoules should be replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

For the sterilization process using an autoclave, details such as F0 range, temperature range and peak dwell time for the FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121˚C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule should be used.

Suitability of the container should be demonstrated, including the following properties.

Safety

- The material must meet compendial requirements such as USP<660> and USP<1660>. Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of the product manufacture

Compatibility

- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers such as PVC may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

The appropriate comparator product is magnesium sulfate 500 mg/mL (solution for injection, Fresenius Kabi, USA). The composition of the proposed product should be the same as the comparator product.

HYDRALAZINE

POWDER FOR INJECTION, 20 MG (HYDROCHLORIDE) IN AMPOULE
TABLETS, 25 MG AND 50 MG (HYDROCHLORIDE)

GENERAL PRODUCT INFORMATION

Hydralazine is a hydrazine derivative vasodilator originally developed as a malaria treatment, however hydralazine showed antihypertensive ability and was soon repurposed.

Hydralazine selectively relaxes arteriolar smooth muscle by an as-yet-unknown mechanism. It is effective orally, intramuscularly, or intravenously; parenteral administration is useful for rapid control of severe hypertension. Hydralazine has been used in all trimesters of pregnancy, and data have not shown an association with teratogenicity, although neonatal thrombocytopenia and lupus have been reported. It has been widely used for chronic hypertension in the second and third trimesters, but its use has been replaced by agents with more favorable adverse effect profiles. For acute severe hypertension later in pregnancy, intravenous hydralazine has been associated with more maternal and perinatal adverse effects therefore, the use of parenteral hydralazine is recognized as a suitable second-line agent.

The WHO's Essential Medicine List (EML) recommends using hydralazine for use in the management of pregnancy-induced hypertension only.

Ciba-Geigy Corporation has successfully registered in 1953 the hydralazine hydrochloride (Apresoline®) in the United States. More recently the product that was owned by Novartis was discontinued in the US, remaining available in few countries as the United Kingdom, Canada and Australia.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by an SRA, and with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is safe for patient use.

3. Regarding the parenteral hydralazine, procurers need to focus on product quality to ensure that it is sterile and safe for patient use as it is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Hydralazine finished product must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

Different packaging configurations are available in the market. The packaging configuration is important to ensure product stability during shelf-life.

Additional information about hydralazine packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Hydralazine powder for injection and tablet are stable when stored below 25°C and do not require cold chain storage.

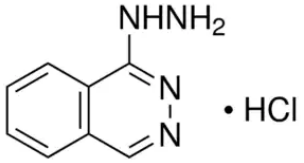
Procurers need to verify with manufacturers that there are satisfactory stability data to support shelf life and storage conditions.

The standard shelf life of hydralazine tablets is 2 to 4 years, depending on the manufacturer, when stored at room temperature.

The standard shelf life of hydralazine powder for injection is 5 years when stored below 25°C and protected from light.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Additional information about the finished product storage requirement can be found in the "Storage, Stability and Degradation" section below.

Name of the Medicinal Product	Hydralazine (hydrochloride)
Chemical Name	phthalazin-1-ylhydrazine; hydrochloride 1-Hydrazinophthalazine monohydrochloride
Chemical Structure	$C_8H_8N_4,HCl$ 
Pharmaceutical Form	Powder for injection: 20 mg (hydrochloride) in ampoule Tablets: 25 mg; 50 mg (hydrochloride)
Qualitative and Quantitative Composition	Powder for injection: – Each 2-mL ampoule contains 20 mg hydralazine hydrochloride. – List of typical excipients[1]: hydrochloric acid for pH adjustment. Tablets: – Each tablet contains 25 mg or 50 mg hydralazine hydrochloride. – List of typical excipients[2]: silicon dioxide, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, maize starch, hydroxypropylmethylcellulose, povidone, talc, titanium dioxide, polyethylene glycol, sucrose, yellow iron oxide, water, shellac glaze, black iron oxide (E172) and propylene glycol (E1520), Red iron oxide (E172), Ammonium Hydroxide (E527).
Packaging and Presentation	Powder for injection: colorless Type I glass 2-mL ampoule. Secondary packaging is normally suitable cardboard to protect from damage. Tablets: polypropylene containers sealed by white polyethylene caps, or amber glass bottles with wadless plastic caps, or PVC/Aluminum blister packs. Secondary packaging is normally suitable cardboard to protect from damage.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

Hydralazine is not included in the WHO PQP. Therefore, no WHO-prequalified hydralazine products are available.

[1] Based on the formulation of an innovator product, Apresoline®
https://mhraproducts4853.blob.core.windows.net/docs/c59f9b08bf4c6d77f6e6df630a4ec6ac415bf4da
[2] Based on the formulation of an innovator product, Apresoline Ampoules 20 mg
https://www.medicines.org.uk/emc/product/6710/smpc

SRA-approved products

Table H-28. Examples of SRA-Approved Hydralazine Powder for Injection

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Apresoline Ampoules 20 mg	MHRA	Amdipharm UK Limited, the UK	PL 20072/0230	Colorless Type I glass 2-mL ampoule.	5 years	Store in original package in order to protect from light. Store below 25 °C. For single use only. Use immediately after reconstitution.
Apresoline 20mg powder for injection ampoule	TGA	Amdipharm Mercury Australia Pty Ltd, Australia	AUST R 43190	Glass ampoules	5 years	Store below 25°C. Protect from light.

Table H-29. Examples of SRA-Approved Hydralazine Tablets

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Apresoline Tablets 25 mg	MHRA	Amdipharm UK Limited, the UK	PL 20072/0026	Securitainers*	4 years	Protect from moisture and heat. Store below 30°C.
Hydralazine 50 mg Film-coated Tablets	MHRA	Generics [UK] Limited t/a Mylan	PL 4569/0051	Polypropylene containers sealed by white polyethylene caps with optional polyethylene ullage fillers or amber glass bottles with wadless plastic caps or PVC/Aluminum blister packs	3 years	Do not store above 25°C. Store in the original package in order to protect from light.
Hydralazine 25 mg Film-coated Tablets	MHRA	Generics [UK] Limited t/a Mylan	PL 04569/0050	Polypropylene containers sealed by white polyethylene caps with optional polyethylene ullage fillers or amber glass bottles with wadless plastic caps or PVC/Aluminum blister packs.	3 years	Do not store above 25°C. Store in the original package in order to protect from light.
Hydralazine 50 mg Tablets BP	MHRA	Accord-UK Ltd	PL 00142/0500	Rigid injection molded polypropylene containers and snap-on polyethylene lids or PVC/Aluminum blister packs.	3 years	Polypropylene containers: Do not store above 25°C. Store in the original container. Blister packs: Do not store above 25°C. Keep container in the outer carton.
Hydralazine 25 mg Tablets BP	MHRA	Accord-UK Ltd	PL 00142/0499	Rigid injection molded polypropylene containers and snap-on polyethylene lids or PVC/Aluminum blister packs.	3 years	Polypropylene containers: Do not store above 25°C. Store in the original container. Blister packs: Do not store above 25°C. Keep container in the outer carton.
Hydralazine 50 mg Tablets	MHRA	Morningside Healthcare Ltd	PL 20117/0259	Alu/Alu cold form film with aluminum lidding foil	2 years	Do not store above 25°C.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Hydralazine 25 mg Tablets	MHRA	Morningside Healthcare Ltd	PL 20117/0258	Alu/Alu cold form film with aluminum lidding foil	2 years	Do not store above 25°C.
Mint-Hydralazine Tablets 50 mg	Health Canada	Mint Pharmaceuticals INC	DIN 02468794	Bottle	Not specified	Store at room temperature (15-30°C). Preserve in tight containers and protect from light.
Mint-Hydralazine Tablets 25 mg	Health Canada	Mint Pharmaceuticals INC	DIN 02468786	Bottle	Not specified	Store at room temperature (15-30°C). Preserve in tight containers and protect from light.
Jamp-Hydralazine Tablets 50 mg	Health Canada	Jamp Pharma Corporation	DIN 02457881	Bottle	Not specified	Store at room temperature (15-30°C). Preserve in tight containers and protect from light.
Jamp-Hydralazine Tablets 25 mg	Health Canada	Jamp Pharma Corporation	DI 0N2457873	Bottle	Not specified	Store at room temperature (15-30°C). Preserve in tight containers and protect from light.
ASN-Hydralazine Tablets 50 mg	Health Canada	Ascend Laboratories LTD	DIN 02493667	Bottle	Not specified	Store at room temperature (15-30°C).
ASN-Hydralazine Tablets 25 mg	Health Canada	Ascend Laboratories LTD	DIN 02493659	Bottle	Not specified	Store at room temperature (15-30°C).
Apo-Hydralazine Tablets 50 mg	Health Canada	Apotex INC	DIN 00441635	Bottle	Not specified	Store at room temperature (15-30°C)
Apo-Hydralazine Tablets 25 mg	Health Canada	Apotex INC	DIN 00441627	Bottle	Not specified	Store at room temperature (15 - 30°C)
Alphapress 50 hydralazine hydrochloride 50mg tablet bottle	TGA	Alphapharm Pty Ltd - Mylan	AUST R 60380	Bottle (HDPE)	3 years	Store below 25°C. Protect from light.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Alphapress 25 hydralazine hydrochloride 25mg tablet bottle	TGA	Alphapharm Pty Ltd – Mylan	AUST R 17575	Bottle (HDPE)	3 years	Store below 25°C. Protect from light.
Hydralazine Hydrochloride 25 mg 50 mg	US-FDA	ScieGen Pharmaceuticals, Inc	ANDA # 205236	Bottle	Not specified	Store at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30° C (59° to 86° F). [See USP Controlled Room Temperature].
Hydralazine Hydrochloride 25 mg 50 mg	US-FDA	Cadila Pharms LTD	ANDA # 203845	Bottle	Not specified	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

** Note: Securitainer® is a security container used as an individual transport container for glass vials and/or as packaging for materials and substances sensitive to dampness.*

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may change over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other formulations of hydralazine that exist in the market include the following products.

- Capsule 25 mg
- Tablets 10 mg; 100 mg
- Solution, Injection, as hydrochloride: 20 mg/mL

It is important to note that the WHO EML recommends hydralazine powder for injection 20 mg (hydrochloride) in ampoule, hydralazine tablets 50 mg (hydrochloride) or 25 mg (hydrochloride) for use in the gestational hypertension. Therefore, the procurement agency must focus on procurement of these presentations as per the WHO EML.

STORAGE, STABILITY, AND DEGRADATION

Powder for injection:
- Hydralazine powder for injection is stable at room temperature and does not require cold chain storage.
- Shelf life: 5 years. It is recommended to check the product label before use.
- Storage conditions: Store below 25°C. Protect from light.

Tablets:
- Hydralazine tablet is stable at room temperature and does not require cold chain storage.
- Shelf life: 2 to 4 years. It is recommended to check the product label before use.
- Storage conditions: Do not store above 25°C. Protect from light.

The shelf life and storage condition of each SRA-approved product can be found in Tables H-1 and H-2.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopeia and British Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Table H-30. British Pharmacopeia Specifications for Hydralazine Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (a) IR	The infrared absorption spectrum is concordant with the reference spectrum of hydralazine hydrochloride.	Appendix II A
(b) UV absorption	The light absorption in the range 230 to 350 nm of a 0.002% w/v solution exhibits four maxima, at 240, 260, 305 and 315 nm.	Appendix II B
(c) Chloride	Yield the reactions characteristic of chlorides	Appendix VI
Acidity	pH of a 2% w/v solution, 3.5 to 4.2	Appendix V L
Clarity of solution	A 2.0% w/v solution is not more opalescent than reference suspension II,	Appendix IV A
Color of solution	A 2.0% w/v solution in 0.01M hydrochloric acid is not more intensely colored than reference solution GY6.	Appendix IV B, Method II.
Hydrazine	Any spot corresponding to hydrazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).	Thin-layer chromatography, Appendix III A
Uniformity of content	Sealed containers each containing 20 mg or less of Hydralazine Hydrochloride comply with the requirements stated under Parenteral Preparations, Powders for Injections or Infusions.	Appendix II B
Assay	98.0 to 114.0% of the stated amount.	Appendix XII C1
Endotoxin	Comply	Appendix XIV C
Particulate matter	Comply	Appendix XIII A
Sterile	Sterile	Appendix XVI A

Table H-31. US Pharmacopeia Specifications for Hydralazine Hydrochloride Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (IR)	The IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as those of USP Hydralazine Hydrochloride RS similarly treated and prepared.	USP ⟨197M⟩
Assay	95.0%–105.0%	Titration as per USP monograph of hydralazine hydrochloride Injection
pH	3.4 – 4.4	USP ⟨791⟩
Endotoxin	Not more than 1.45 USP Endotoxin Units/mg	USP ⟨85⟩
Particulate matter in injections	Meets the requirements for small-volume injections	USP ⟨788⟩
Sterility	Must be sterile	USP ⟨71⟩

Note: The USP specifications described in table H-4 refers to the hydralazine hydrochloride solution. When applying to the hydralazine hydrochloride powder for injection, the product needs to be reconstituted in Water for Injection (WFI) before testing.

In addition to the tests mentioned in the product monograph, the following tests needs to be considered for parenteral powder for reconstitution:

- Uniformity of content.
- Water content - loss on drying is generally considered sufficient for parenteral products, if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development. In certain cases, a more specific procedure (e.g., Karl Fischer titration) may be preferred.
- Reconstitution time: as defined in the ICH Q6A, acceptance criteria for reconstitution time should be provided for all parenteral products that require reconstitution. This attribute can be excluded from the specification for rapidly dissolving products.

Table H-32. US Pharmacopeia Specifications for Hydralazine Hydrochloride Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (a) Infrared spectroscopy	Meet the requirements	USP ⟨197K⟩
(b) HPLC	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay.	HPLC, USP ⟨621⟩
Assay	90.0%–110.0%	HPLC, USP ⟨621⟩
Dissolution	Not less than 75% (Q) of the labeled amount of hydralazine hydrochloride is dissolved.	USP ⟨711⟩
Uniformity of dosage units	Meet the requirements	USP ⟨905⟩
Organic impurities	Any unspecified degradation product: Not more than 0.20% Total impurities: Not more than 1.5%	HPLC, USP ⟨621⟩

Table H-33. British Pharmacopeia Specifications for Hydralazine Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (a) IR	The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of hydralazine.	Appendix II A
(b) UV absorption	The light absorption in the range 230 to 350 nm exhibits four maxima, at 240, 260, 305 and 315 nm.	Appendix II B
(c) Chemical test	An orange precipitate is produced.	As per BP monograph of hydralazine tablets
Hydrazine	Any spot corresponding to hydrazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2).	Thin-layer chromatography, Appendix III A
Assay	95.0 to 105.0% of the stated amount	Titration as per BP monograph of hydralazine tablets
Dissolution	Meet the requirements **	Appendix XII B
Uniformity of dosage units	Meet the requirements	Appendix XII C

***Note: the hydralazine tablet should comply with the requirements for the general chapter on 'tablets' that specifies the dissolution test as a requirement. If the manufacturer claims that hydralazine is BSC class III, the dissolution specification needs to be specified as Q=80% in 15 minutes.*

HYDRALAZINE ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Hydralazine is indicated for use in the acute management of severe pregnancy-induced hypertension only.

Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

The sterile injectable form is used to lower blood pressure primarily in pregnant women suffering from severe preeclampsia and eclampsia in hypertensive crisis situations. The oral tablet form of hydralazine hydrochloride is used in patients requiring long-term management of their hypertension after such a crisis has abated.

Posology, method, and duration of administration

Injection

Initially 5 to 10 mg by slow intravenous injection, to avoid precipitous decreases in arterial pressure with a critical reduction in cerebral or utero-placental perfusion. If necessary, a repeat injection can be given after an interval of 20-30 minutes, throughout which blood pressure and heart rate should be monitored. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90/100 mmHg. The contents of the ampoule should be reconstituted by dissolving in 1 ml of water for injection BP. This should then be further diluted with 10 ml of Sodium Chloride injection BP 0.9% and be administered by slow intravenous injection. The injection must be given immediately, and any remainder discarded. Hydralazine may also be given by continuous intravenous infusion, beginning with a flow rate of 200-300µg/min. Maintenance flow rates must be determined individually and are usually within the range 50-150µg/min. The product reconstituted as for direct IV injection may be added via the infusion container to 500 ml of Sodium Chloride Injection BP 0.9% and given by continuous infusion. The addition should be made immediately before administration and the mixture should not be stored. Hydralazine for infusion can also be used with 5% sorbitol solution or isotonic inorganic infusion solutions such as Ringer's solution.

Tablets

The initial dose is 25 mg twice daily. This may be increased gradually to a maximum dose of 200 mg daily. The patient's acetylator status must be checked prior to increasing the daily dose beyond 100 mg.

Contraindications

Hydralazine is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients;
- Known hypersensitivity to hydralazine or dihydralazine or to any of the excipients;

- Idiopathic systemic lupus erythematosus (SLE) and related diseases;
- High output cardiac failure (e.g. in thyrotoxicosis);
- Myocardial insufficiency due to mechanical obstruction (e.g. in the presence of aortic or mitral stenosis or constrictive pericarditis);
- Isolated right ventricular failure due to pulmonary hypertension (cor pulmonale);
- Dissecting aortic aneurysm;
- Porphyria.

Special warnings and precautions for use

Warnings

The overall 'hyperdynamic' state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris. Patients with suspected or confirmed coronary artery disease should therefore be given Hydralazine only under beta-blocker cover or in combination with other suitable sympatholytic agents. Beta-blocker medication should be started a few days prior to commencing treatment with Hydralazine.

Patients who have survived a myocardial infarction should not receive Hydralazine until a post-infarction stabilization phase has been achieved.

Prolonged treatment with hydralazine (i.e. usually for more than 6 months) may provoke a systemic lupus erythematosus (SLE)-like syndrome, especially with doses exceeding 100 mg daily. First symptoms are likely to be similar to rheumatoid arthritis (arthralgia, sometimes associated with fever, anemia, leucopenia, thrombocytopenia and rash) and are reversible after withdrawal of the drug. In its more severe form it resembles acute SLE (similar manifestations as the milder form plus pleurisy, pleural effusions and pericarditis), and in rare cases renal and ocular involvement have been reported. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids may be required to reverse these changes) are of utmost importance in this life-threatening illness to prevent more severe complications, which may sometimes be fatal.

Since such reactions tend to occur more frequently as the treatment dose and duration increase, and since they are more common in slow acetylators, it is recommended that for maintenance therapy the lowest effective dose should be used. If 100 mg daily fails to elicit an adequate clinical effect, the patient's acetylator status should be evaluated. Slow acetylators and women run greater risk of developing the SLE like syndrome and every effort should therefore be made to keep the dosage below 100 mg daily and a careful watch kept for signs and symptoms suggestive of this syndrome. If such symptoms do develop, the drug should be gradually withdrawn. Rapid acetylators often respond inadequately even to doses of 100 mg daily and therefore the dose can be raised with only a slightly increased risk of an SLE-like syndrome.

During long term treatment with Hydralazine, it is advisable to determine the antinuclear factors and conduct urine analysis at intervals of approximately 6 months. Microhematuria and / or proteinuria, in particular together with positive titers of ANF, may be initial signs of immune-complex glomerulonephritis associated with the SLE like syndrome. If overt clinical signs or symptoms develop, the drug should be withdrawn immediately.

Skin rash, febrile reactions and changes in blood count occur rarely and in these cases the drug should be withdrawn. Peripheral neuritis in the form of paresthesia has been reported and may respond to pyridoxine administration or withdrawal of the drug.

In high (cyto-) toxic concentrations, hydralazine induces gene mutations in single cell organisms and in mammalian cells in vitro. No unequivocally mutagenic effects have been detected in vivo in a great number of test systems.

Hydralazine in lifetime carcinogenicity studies, caused, towards the end of the experiments, small but statistically significant increases in lung tumors in mice and in hepatic and testicular tumors in rats. These tumors also occur spontaneously with fairly high frequency in aged rodents.

With due consideration of these animals and in-vitro toxicological findings, hydralazine in therapeutic doses does not appear to bear risk that would necessitate a limitation of its administration. Many years of clinical experience have not suggested that human cancer is associated with hydralazine use.

Precautions

In patients with renal impairment (creatine clearance < 30 ml/min or serum creatinine concentrations> 2.5 mg / 100 ml or 221 µmol / l) and in patients with hepatic dysfunction the dose or interval between doses should be adjusted according to clinical response, to avoid accumulation of the 'apparent' active substance.

Hydralazine should be used with caution in patients with coronary artery disease (since it may increase angina) or cerebrovascular disease.

When undergoing surgery, patients treated with Hydralazine may show a fall in blood pressure, in which case one should not use adrenaline to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine.

When initiating therapy in heart failure, particular caution should be exercised, and the patient monitored for early detection of postural hypotension or tachycardia. Where discontinuation of therapy in heart failure is necessary, Hydralazine should be withdrawn gradually (except in serious situations such as SLE-like syndrome or blood dyscrasias) to avoid precipitation and /or exacerbation of heart failure.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction

Potentiation of effects: Concurrent therapy with other antihypertensives (vasodilators, calcium antagonists, ACE inhibitors, diuretics), anesthetics, tricyclic antidepressants, major tranquillizers, nitrates or drugs exerting central depressant actions (including alcohol).

Administration of Hydralazine shortly before or after diazoxide may give rise to marked hypotension.

MAO inhibitors should be used with caution in patients receiving Hydralazine.

Concurrent administration of Hydralazine with beta-blockers subject to a strong first pass effect (e.g. propranolol) may increase their bioavailability. Download adjustment of these drugs may be required when they are given concomitantly with Hydralazine.

There is potential for the hypotensive effect of hydralazine to be antagonized when used concomitantly with estrogens or combined oral contraceptive, corticosteroids, carbenoxolone or non-steroidal anti-inflammatory drugs, specially indometacin.

Pregnancy and lactation

Pregnancy

Use of Hydralazine in pregnancy, before the third trimester should be avoided but the drug may be employed in later pregnancy if there is no safer alternative or when the disease itself carries serious risks for the mother or child e.g. pre-eclampsia and /or eclampsia.

Hydralazine readily crosses the placenta with serum concentrations in the fetus being equal to or greater than those in the mother. No serious adverse effects in human pregnancy have been reported with hydralazine use during the third trimester. Thrombocytopenia, leucopenia, petechial bleeding and hematomas have been reported in newborns whose mother took hydralazine, though these symptoms resolved spontaneously in one to three weeks.

Breastfeeding

Hydralazine passes into breast milk but reports available so far have not shown adverse effects on the infant. Mothers in whom use of Hydralazine proves unavoidable may breastfeed their infant provided that the infant is observed for possible adverse effects.

Effects on ability to drive and use machines

Hydralazine may impair the patient's reactions especially at the start of the treatment. The patient should be warned of the hazard when driving or operating machinery.

Undesirable effects

Some of the adverse effects listed below e.g. tachycardia, palpitations, angina symptoms, flushing, headache, dizziness, nasal congestion and gastro-intestinal disturbances are commonly seen at the start of treatment, especially if the dose is raised quickly. However, such effects generally subside in the further course of treatment.

The following frequency estimates are used: Very common (≥ 1/10), common (≥ 1/100, < 1/10), rare (≥ 1/10000, < 1/1000); isolated cases (< 0.001%).

- Cardiovascular system:
  - Very common: tachycardia, palpitations.
  - Common: flushing, hypotension, anginal symptoms.
  - Rare: oedema, heart failure.
  - Isolated cases: paradoxical pressor responses.
- Central and peripheral nervous system:
  - Very common: headache.
  - Rare: dizziness.
  - Isolated cases: peripheral neuritis, polyneuritis, paresthesia (these unwanted effects may be reversed by administering pyridoxine).
- Musculo-skeletal system:
  - Common: arthralgia, joint swelling, myalgia, SLE-like syndrome (sometimes resulting in a fatal outcome)
- Skin and appendages:
  - Rare: rash.
- Urogenital system:
  - Rare: proteinuria, increased plasma creatinine, hematuria sometimes in association with glomerulonephritis.

- Isolated cases: acute renal failure, urinary retention.

- Gastrointestinal tract:
  - Common: gastrointestinal disturbances, diarrhea, nausea, vomiting.
  - Rare: jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis.
  - Isolated cases: paralytic ileus.
- Hepatobiliary disorders:
  - Rare: jaundice, hepatomegaly, abnormal liver function sometimes in association with hepatitis.
- Blood:
  - Rare: anemia, leucopenia, neutropenia, thrombocytopenia with or without purpura.
  - Isolated cases: hemolytic anemia, leukocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis.
- Psychiatric reactions:
  - Rare: agitation, anorexia, anxiety.
  - Isolated cases: depression, hallucinations.
- Sense organs:
  - Rare: increased lacrimination, conjunctivitis, nasal congestion.
- Hypersensitivity reactions:
  - Common: SLE-like syndrome that eventually could result in a fatal outcome.
  - Rare: hypersensitivity reactions such as pruritus, urticaria, vasculitis, eosinophilia, hepatitis.
- Respiratory tract:
  - Common: nasal congestion
  - Rare: dyspnea, pleural pain.
- Miscellaneous:
  - Rare: fever, weight decrease, malaise, increased lacrimation, conjunctivitis.
  - Isolated cases: exophthalmos.

Overdose

Symptoms

Symptoms include hypotension, tachycardia, headache and generalized skin flushing. Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmias, profound shock and coma.

Treatment

Support of the cardiovascular system is of primary importance. Supportive measures including intravenous fluids are also indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. If a vasopressor is used, one should be chosen that is least likely to precipitate or aggravate cardiac arrhythmia. Tachycardia responds to beta-blockers. Digitalization may be necessary. Fluid and electrolyte status and renal function should be monitored. Adrenaline should therefore be avoided.

If overdose happens after administration of tablets, gastric lavage should be instituted as soon as possible, taking adequate precautions against aspiration and for protection of the airway. An activated charcoal slurry may be instilled if conditions permit. These procedures may have to be omitted or carried out after cardiovascular status has been stabilized since they might precipitate cardiac arrhythmias or increase the depth of shock.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full evaluation of hydralazine products. When assessing the complete quality/CMC documentation, assessors should consider the following information on hydralazine tablets and powder for injection.

API

Hydralazine is not included in the WHO PQP. Therefore, there is no WHO-prequalified hydralazine API.

Five manufacturers of hydralazine API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Table H-34. Manufacturers of Hydralazine API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Hydralazine hydrochloride (monograph number 829)	Macleods Pharmaceuticals Limited Mumbai, IN	R0-CEP 2016-180-Rev 00	3/16/2018	Chemistry
Hydralazine hydrochloride (monograph number 829)	Archimica S.P.A Lodi, IT	R0-CEP 2015-161-Rev 01	10/29/2020	Chemistry
Hydralazine hydrochloride (monograph number 829)	Solara Active Pharma Sciences Limited Chennai, IN	R1-CEP 2013-191-Rev 01	3/2/2021	Chemistry
Hydralazine hydrochloride (monograph number 829)	Sumitomo Chemical Company Limited Osaka, JP	R0-CEP 2018-170-Rev 02	3/21/2022	Chemistry
Hydralazine hydrochloride (monograph number 829)	Hetero Labs Limited Hyderabad, IN	R0-CEP 2018-287-Rev 01	5/24/2022	Chemistry

Other manufacturers of hydralazine API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines[1].

Hydralazine API must meet pharmacopeia specifications such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.

Hydralazine API is known to be thermolabile and humidity sensitive. Therefore, the management of the temperature and humidity and the way to prevent the API from predictive degradation all along the manufacturing channels is important and should consider:

- Recording temperature during transportation of the API.
- Reception and weighing of the products (climatization of the storage area temperature and humidity).
- Checking the conditions of the bag sealing after opening the API bag.

Excipients

Excipients must conform to pharmacopeia monographs.

Some papers suggest potential incompatibility of hydralazine with sugars (e.g. sucrose, dextrose, aldose, ketose sugar, lactose, fructose and maltose) that may result in osazones presence. The comparator product Apresoline® contains sucrose. Alexander at al[2] has found that unhydrolyzed sucrose seems not to have a significant interaction with hydralazine. Therefore, if sucrose is considered as part of the formulation, its technical grade needs to be specified and its stability with the API needs to be carefully assessed. If included in the formulation, it is recommended that the amount of sucrose is the same as present in the comparator product.

Hydralazine reacts with metal ions (chelate metal ions). Hydralazine oxidizes rapidly in the presence of oxygen and metal ions such as Cu+2, Fe+2, and Fe+3 through free radical intermediates.

Hydralazine hydrochloride also undergoes pH-dependent decomposition. These reactions often cause discoloration of hydralazine compositions. Hydrolysis takes place by water attack on the dicationic and the cationic forms of the drug. Additional degradation may happen via hydroxyl attack on the cationic and the neutral forms of the drug. The drug is not subject to attack by acetate and carbonate buffers, but its decomposition is catalyzed by phosphate buffer system. The pH profile indicates that hydralazine has maximum stability near pH 3.5.

Hydralazine hydrochloride is not compatible with edetate sodium and sodium bisulfite. Available studies indicate that on contact, the solution turns yellow immediately and at one week the loss of drug was 29% and 80%, in presence of edetate sodium and sodium bisulfite respectively.

These factors need to be considered when selecting the formulation.

When colorants are included in the formulation, the type and amount used should comply with the regulations of the country to be marketed. Different authorities may have different restrictions. For example, some colorants, such as FD&C Yellow No. 6, included in the FDA-approved products may require reduced quantity when registered in Europe due to toxicology concern.[3]

[2] Alexander, KS., Pudipeddi, M, Parker GA. 1993. "Stability of hydralazine hydrochloride syrup compounded from tablets." *Am J Hosp Pharm* 50(4): 683-6. Erratum in: *Am J Hosp Pharm* 1993; 50(10): 2057. PMID: 8470684.

[3] European Food Safety Authority, 2009. "Scientific Opinion on the re-evaluation of Sunset Yellow FCF (E 110) as a food additive". Available at: https://www.efsa.europa.eu/fr/efsajournal/pub/1330

Manufacturing process

Powder for injection

Hydralazine hydrochloride may be sensitive to prolonged exposure to high temperature, humidity and light. Therefore, environmental conditions during manufacturing should be defined considering these risks.

The manufacturing process needs to be conducted under appropriate aseptic conditions, including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, filling and sealing of the ampoules and lyophilization. The replacement of the headspace of the ampoules with nitrogen is recommended to prevent oxidation of the API.[4] Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

The filters used in the sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components.

The filling of units that are to be lyophilized needs to be carefully controlled as the stopper is placed on top of the flask (partially stoppered) and is ultimately seated in the lyophilizer. As a result, the product is potentially subject to contamination until they are actually sealed. Validation of filling operations and filled flasks handling should include media fills and the sampling of critical surfaces and air during active filling, transportation and lyophilizer loading (dynamic conditions).

The lyophilization is a complex process that requires careful development and validation support. Key parameters to be observed include: shelf temperature, product temperature, chamber pressure, secondary drying times, etc. These parameters need to be specified in the protocols and should comply with process validation requirements. Sometimes these process parameters may change from time to time based on the process dynamics and hence may require regular verification. The sterilization of the lyophilizer is also a concern and requires proper validation.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Tablet

Hydralazine hydrochloride tablets should be manufactured according to recognized principles of GMP using ingredients that comply with specifications designed to ensure the final products meet the requirements of the compendial monographs.

Hydralazine hydrochloride may be sensitive to prolonged exposure to high temperature, humidity and light. Therefore, environmental conditions during manufacturing should be defined considering these risks.

[4] Salma Imad, Shazia Nisar, Zahida T. Maqsood. 2010. "A study of redox properties of hydralazine hydrochloride, an antihypertensive drug." Journal of Saudi Chemical Society 14(3): 241-245. PMID: 8470684; DOI:10.1016 / j.jsc.2010.02.003. Available at: https://www.researchgate.net/publication/250780142_A_study_of_redox_properties_of_hydralazine_hydrochloride_an_antihypertensive_drug

The manufacturing process is usually carried out by direct tableting method. Aiming to increase the product stability, the tablets are coated. Due to the instability of hydralazine, manufacturing process including wet granulation and drying steps must be avoided.

If coating is applied, processes where the temperature is low (below 50°C) and the process is short are preferred. The presence of lactose and sucrose in the filming agents needs to be avoided.

The uniformity of the batch used in biowaiver or bioavailability studies should be provided. In addition, a manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In the case where the manufacturer is already manufacturing production-scale batches, the full validation data for at least three consecutive production scale batches should be submitted.

Notes:

- The risk *for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed.* Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.[5,6]

Packaging

Powder for injection

Neutral type I glass ampoule should be used.

Suitability of the container should be demonstrated, including:

Safety

- Glass ampoules must meet compendial requirements such as USP<660> and USP<1660>.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:

- One-time test reported as part of product development
- Routine leak testing performed as part of product manufacture

Compatibility

[5] WHO, 2019. "Information Note: Nitrosamine impurities". Available at: https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[6] WHO, 2021. "Nitrosamine concerns in rifampicin products – Update". Available at: https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

- Compatibility of the FPP with diluents (such as 0.9% sodium chloride, 5% sorbitol solution or Ringer's solution as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers may also need to be demonstrated.

Tablets

Suitability of the container should be demonstrated, including:

Safety

- Blister: Declarations as to compliance with appropriate food additive regulations (e.g., US FDA or EU regulations).
- Glass/plastic bottles: food grade declaration and tests as per USP<660>/Ph.Eur. 3.2.1 (Glass); USP<661>/Ph.Eur. 3.1.10 (Plastics).

Protection

- Blister: Water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671> Compatibility.
- Glass/plastic bottles: plastics: WVTR (weight loss) and LT as per USP<671>.

Compatibility

- Accelerated and long-term stability data for the packaged finished products.

Bioequivalence requirements

Powder for injection

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is in the form of powders for reconstitution as an aqueous solution and the resulting solution is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

An appropriate comparator product is Apresoline® 20mg powder for injection. The composition of the proposed product should be the same as the comparator product.

Tablet

Bocci at al[7] reported that hydralazine hydrochloride is a BCS Class III drug (High Solubility / Low Permeability (HS/LP)). It could be eligible for a biowaiver provided:

1. Both the multisource and the comparator products are very rapidly dissolving – 85% or more dissolution of the labelled amount of the API should be achieved within 15 minutes or less in standard media at pH 1.2, 4.5 and 6.8 (as defined below);
2. The dosage form does not contain any inactive ingredients that are known to alter GI motility and permeability.

[7] Bocci, G., Oprea, TI., Benet, LZ. 2022. "State of the Art and Uses for the Biopharmaceutics Drug Disposition Classification System (BDDCS): New Additions, Revisions, and Citation References." *AAPS J* 24(2): 37. doi: 10.1208/s12248-022-00687-0. PMID: 35199251; PMCID: PMC8865883.

Note: Since hydralazine hydrochloride is not included in the current WHO biowaiver list[8], the manufacturer applying for biowaiver can be requested to submit data from the solubility and permeability studies to demonstrate its high solubility and low permeability as per the BCS Class III definition.

Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 15 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Pharmacopeial buffers (e.g., Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media.

It should be demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g., by effects on gastrointestinal motility or interactions with transport processes) or that might lead to interactions that alter the pharmacokinetics of the API.

An appropriate comparator product is Apresoline® Tablets 25 mg. It is therefore recommended that the excipients employed be present in the comparator product, or be present in other products that contain the same API as the multisource product and that have marketing authorizations in ICH-associated countries. Excipients that might affect the bioavailability of the API (e.g., mannitol, sorbitol, or surfactants), should be identified and an assessment of their impact provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

[8] WHO. 2021. "WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms," Annex 8 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 55th report. Technical Report Series No. 1003. Geneva: WHO.

METHYLDOPA

TABLETS, 250 MG

GENERAL PRODUCT INFORMATION

Methyldopa is a centrally-acting alpha-2 adrenergic agonist used to manage pregnancy-induced hypertension. The WHO recommendations on the use of antihypertensive drugs for non-severe hypertension in pregnancy[1] states that oral methyldopa should be considered as an effective treatment option for non-severe hypertension during pregnancy. When compared with other antihypertensives, methyldopa has the fewest safety concerns and is therefore listed for use as an antihypertensive agent during pregnancy in the WHO Model List of Essential Medicines. Methyldopa is available worldwide.

Based on the available evidence, the WHO recommendations on drug treatment for severe hypertension in pregnancy[2] states that methyldopa has been extensively used, and therefore is a reasonable choice until further evidence becomes available.

The WHO's Essential Medicine List (EML) recommends using methyldopa for use in the management of pregnancy-induced hypertension only.

[1] WHO. 2020. WHO recommendations on drug treatment for non-severe hypertension in pregnancy. Geneva: WHO. Licence: CC BY-NC-SA 3.0 IGO. Available at https://apps.who.int/iris/bitstream/handle/10665/333816/9789240008793-eng.pdf?sequence=1&isAllowed=y

[2] WHO. 2018. WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: WHO. Licence: CC BY-NC-SA 3.0 IGO. Available at https://apps.who.int/iris/bitstream/handle/10665/277234/9789241550437-eng.pdf?ua=1

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by an SRA, and with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is safe for patient use.

KEY QUALITY CONSIDERATIONS

Product specification

Methyldopa finished product must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

Different packaging configurations are available in the market. The packaging configuration is important to ensure the product stability during shelf-life. The packaging system should ensure that the product is protected from light.

Additional information about methyldopa packaging and labeling can be found in the Annex.

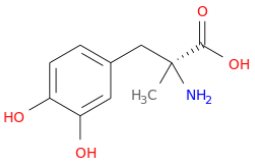
Storage, transportation, and distribution

Methyldopa tablet is stable at room temperature and does not require cold chain storage.

Procurers need to verify with manufacturers that there are satisfactory stability data to support shelf life and storage conditions. The standard shelf life of methyldopa tablets is three years when stored at room temperature.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Additional information about the finished product storage requirement can be found in the "Storage, Stability and Degradation" section below.

Name of the Medicinal Product	Methyldopa tablets 250 mg
Chemical Name Chemical Structure	(2S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid $C_{10}H_{13}NO_4$ 
Pharmaceutical Form	Film-coated tablets
Qualitative and Quantitative Composition	Each tablet contains methyldopa (as sesquihydrate) equivalent to 250 mg methyldopa anhydrous. List of typical excipients[3]: Tablet-core: – Powdered cellulose – Citric acid anhydrous – Colloidal anhydrous silica – Ethylcellulose – Guar gum – Magnesium stearate – Sodium calcium edetate Tablet-coating: – Propylene glycol – Citric acid monohydrate – Hypromellose – Coloring agents (iron oxide red, quinoline yellow aluminum lake) – Purified talc – Titanium dioxide – Carnauba wax Other SRA-approved formulations may include: Povidone, crospovidone, sodium starch glycollate, sodium edetate, precipitated silica, macrogol, stearic acid, microcrystalline cellulose, coloring agents.
Packaging and Presentation	Typically, white polyethylene bottle with polyethylene closure, or PVC/aluminum blister packs are used for primary packaging. Secondary packaging is normally suitable cardboard to protect from damage.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

[3] Based on the formulation of an innovator product, Aldomet®
(https://mhraproducts4853.blob.core.windows.net/docs/7538b51f7a6db9c8006c7dcfed40155a032db357)

WHO-prequalified products

Methyldopa is not included in the WHO PQP. Therefore, no WHO-prequalified methyldopa products are available.

SRA-approved products

Table MD-35. Examples of SRA-Approved Methyldopa 250 mg Tablets.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Methyldopa	US FDA	Accord Hlthcare, USA	ANDA # 070084	Bottle	Not specified	Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature]. Protect from light.
Methyldopa	Health Canada	AA Pharma Inc, Canada	00360260	Bottle	Not specified	Not specified
Hydopa® methyldopa (as sesquihydrate) 250 mg tablet bottle	TGA	Alphapharm Pty Ltd, Australia	AUST R 69482	HDPE bottle	3 years	Store below 25°C.
Aldomet® methyldopa (as sesquihydrate) 250 mg tablet bottle	TGA	Aspen Pharmacare Australia Pty Ltd, Australia	AUST R 34361	White HDPE bottle	3 years	Store below 30°C.
Aldomet® Tablets 250 mg	UK MHRA	Aspen Pharma Trading Ltd, Ireland	PL 39699/0053	White polyethylene bottle with turquoise polyethylene closure, or PVC/aluminum blister packs	3 years	Keep containers well closed and store below 25°C, protected from light.
Methyldopa Tablets BP 250 mg	UK MHRA	Accord-UK Ltd, UK	PL 00142/0093	Rigid injection molded polypropylene or injection blow-molded polyethylene containers and snap-on polyethylene lids	3 years	Store below 25°C in a dry place. Protect from light.
Methyldopa 250 mg Tablets	UK MHRA	Waymade plc Trading as Sovereign Medical, UK	PL 06464/1433	PVC/Aluminum Blisters packs	3 years	Do not store above 25°C and store in the original container.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Methyldopa Tablets BP 250 mg	UK MHRA	Relonchem Ltd, UK	PL 20395/0110	Polypropylene securitainers with appropriate bellows or polyurethane foam wads	3 years	Store below 25°C in a dry place. Protect from light.
Methyldopa Tablets 250 mg	UK MHRA	Crescent Pharma Ltd, UK	PL 20416/0405	Opaque plastic container composed of high-density polyethylene with a child resistant tamper evident closure composed of high-density polyethylene	3 years	Protect from heat, light and moisture. Store in the original container.
Methyldopa 250 mg Tablets BP	UK MHRA	Bristol Laboratories Ltd, UK	PL 17907/0350	Polypropylene securitainer with high density polyethylene cap and silica gel sachet enclosed, or white opaque PVC/PVdC//Al blister pack.	3 years	Do not store above 25°C. Store in the original container. Keep the container tightly closed.
Methyldopa Tablets 250 mg	UK MHRA	Ennogen Pharma Ltd, UK	PL 40147/0056	Securitainers*.	3 years	Store below 25°C. Protect from light.

** Note: Securitainer® is a security container used as an individual transport container for glass vials and/or as packaging for materials and substances sensitive to dampness.*

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- UK MHRA: https://products.mhra.gov.uk/
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects GMP-compliant manufacturers via tenders (UNICEF contract award) to supply products to UNICEP usually over a two- or three-year period.

[1] The selected manufacturers can be considered as trusted sources as they have passed the assessment of UNICEF's quality assurance team.

The most recent list of methyldopa tablets' manufacturers that were granted contract award by UNICEF Supply Division was from 2019 and included the following manufacturers:

- Macleods Pharmaceuticals Limited, India
- Medopharm Private Limited, India
- SM Pharmaceuticals Sdn. Bhhd., Malaysia

It is recommended to check for updated information on the UNICEF website at the time of procurement.

Related products

Other formulations of methyldopa that exist in the market include the following products.

- Film-coated tablets 125 mg

[1] https://www.unicef.org/supply/contract-awards

- Film-coated tablets 500 mg
- Solution, Intravenous, as hydrochloride: 250 mg/5 mL

It is important to note that the WHO EML recommends methyldopa 250 mg for use in the management of pregnancy-induced hypertension. Therefore, the procurement agency must focus on procurement of this presentation as per the WHO EML.

STORAGE, STABILITY, AND DEGRADATION

Methyldopa tablet is stable at room temperature and does not require cold chain storage.

Shelf life: 3 years. It is recommended to check the product label before use.

Storage conditions: Do not store above 25°C. Protect from light.

The shelf life and storage condition of each SRA-approved product can be found in Table MD-1.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopeia and British Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Table MD-36. US Pharmacopeia Specifications for Methyldopa Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (a)	A dark purple color is produced within 5–10 min that changes to pale brownish yellow on addition of 3 drops of water.	As per USP monograph of methyldopa tablets
Identification (b)	A dark purple color is produced immediately.	As per USP monograph of methyldopa tablets
Assay	90.0%–110.0%	Spectrophotometry UV-Vis, as per USP monograph of methyldopa tablets
Dissolution	Not less than 80% (Q) of the labeled amount of methyldopa is dissolved in 20 minutes	USP ⟨711⟩
Uniformity of dosage units	Meet the requirements	USP ⟨905⟩

Table MD-37. British Pharmacopeia Specifications for Methyldopa Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification IR	The infrared absorption spectrum is concordant with the reference spectrum of methyldopa	Appendix II A
TLC	The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2)	Appendix III A
Chemical test	When adding iron (III) chloride solution to hydrochloric acid, a green color is produced. To half of the solution, when adding ammonia, a purple color is produced. When adding sodium hydroxide to the remainder of the solution, a red color is produced.	As per BP monograph of methyldopa tablets
Optical rotation	The optical rotation of the solution prepared as per BP monograph of methyldopa tablets at 25oC is -0.98o to -1.09o	Appendix V F
Assay	95.0 to 105.0% of the stated amount	Appendix II B
Dissolution	Meet the requirements*	Appendix XII B
Uniformity of dosage units	Meet the requirements	Appendix XII C

**Note: Methyldopa tablet should comply with the requirements for the general chapter on 'tablets' that specifies the dissolution test as a requirement. If the manufacturer claims that methyldopa is BSC class III, the dissolution specification needs to be specified as Q=80% in 15 minutes.*

METHYLDOPA ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Methyldopa is indicated for the treatment of hypertension. The WHO EML lists methyldopa for the management of pregnancy induced hypertension only.

Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

Posology, method, and duration of administration

Pregnancy induced hypertension

- 250 to 8000 mg/day (divided between one to four doses per day).

Note: for hypertension control in adults, it is recommended to adjust the dose regimen considering initially, 250 mg 2 or 3 times daily for 2 days and then increase or decrease dosage every 2 days until an adequate response is achieved.

Contraindications

Methyldopa is contraindicated in patients with:

- Active hepatic disease (such as acute hepatitis and active cirrhosis);
- Hypersensitivity to the active substance (including hepatic disorders associated with previous methyldopa therapy) or to any of the excipients included in the formulation;
- A catecholamine-secreting tumor such as phaeochromocytoma or paraganglioma;
- Depression;
- Therapy with monoamine oxidase inhibitors (MAOIs);
- Porphyria.

Special warnings and precautions for use

Acquired hemolytic anemia has occurred rarely; should symptoms suggest anemia, hemoglobin and/or hematocrit determinations should be made. If anemia is confirmed, tests should be done for hemolysis. If hemolytic anemia is present, methyldopa should be discontinued. Stopping therapy, with or without giving a corticosteroid, has usually brought prompt remission. Rarely, however, deaths have occurred.

Some patients on continued therapy with methyldopa develop a positive Coombs test. From the reports of different investigators, the incidence averages between 10% and 20%. A positive Coombs test rarely develops in the first six months of therapy, and if it has not developed within 12 months,

it is unlikely to do so later during continuing therapy. Development is also dose-related, the lowest incidence occurring in patients receiving 1 g or less of methyldopa per day. The test becomes negative usually within weeks or months of stopping methyldopa.

Prior knowledge of a positive Coombs reaction will aid in evaluating a crossmatch for transfusion. If a patient with a positive Coombs reaction shows an incompatible minor crossmatch, an indirect Coombs test should be performed. If this is negative, transfusion with blood compatible in the major crossmatch may be carried out. If positive, the advisability of transfusion should be determined by a hematologist.

Reversible leukopenia, with primary effect on granulocytes has been reported rarely. The granulocyte count returned to normal on discontinuing therapy. Reversible thrombocytopenia has occurred rarely.

Occasionally, fever has occurred within the first three weeks of therapy, sometimes associated with eosinophilia or abnormalities in liver-function tests. Jaundice, with or without fever, may also occur. Its onset is usually within the first two or three months of therapy. In some patients the findings are consistent with those of cholestasis. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy, performed in several patients with liver dysfunction, showed a microscopic focal necrosis compatible with drug hypersensitivity. Liver-function tests and a total and differential white blood-cell count are advisable before therapy and at intervals during the first six weeks to twelve weeks of therapy, or whenever an unexplained fever occurs.

Should fever, abnormality in liver function, or jaundice occur, therapy should be withdrawn. If related to methyldopa, the temperature and abnormalities in liver function will then return to normal. Methyldopa should not be used again in these patients. Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction.

Patients may require reduced doses of anesthetics when on methyldopa. If hypotension does occur during anesthesia, it can usually be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa.

Dialysis removes methyldopa; therefore, hypertension may recur after this procedure.

Rarely, involuntary choreoathetotic movements have been observed during therapy with methyldopa in patients with severe bilateral cerebrovascular disease. Should these movements occur, therapy should be discontinued.

Interference with laboratory tests

Methyldopa may interfere with the measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and AST (SGOT) by colorimetric method. Interference with spectrophotometric methods for AST (SGOT) analysis has not been reported.

As methyldopa fluoresces at the same wavelengths as catecholamines, spuriously high amounts of urinary catecholamines may be reported interfering with a diagnosis of catecholamine-secreting tumors such as phaeochromocytoma or paraganglioma.

It is important to recognize this phenomenon before a patient with a possible phaeochromocytoma is subjected to surgery. Methyldopa does not interfere with measurements of VMA (vanillylmandelic acid) by those methods which convert VMA to vanillin. Methyldopa is contraindicated for the treatment of patients with a catecholamine-secreting tumor such as phaeochromocytoma or paraganglioma.

Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

Interaction with other medicinal products and other forms of interaction

Lithium

When methyldopa and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity.

Other antihypertensive drugs

When methyldopa is used with other antihypertensive drugs, potentiation of antihypertensive action may occur. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy.

Iron

Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulphate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa.

Other classes of drug

The antihypertensive effect of methyldopa may be diminished by sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs. In addition, phenothiazines may have additive hypotensive effects.

Pregnancy and lactation

Pregnancy

Methyldopa has been used under close medical supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that methyldopa caused fetal abnormalities or affected the neonate.

Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of fetal harm appears remote.

Methyldopa crosses the placental barrier and appears in cord blood.

Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded and the use of the drug in women who are, or may become pregnant requires that anticipated benefits be weighed against possible risks.

Breast-feeding

Methyldopa appears in breast milk. The use of the drug in breast-feeding mothers requires that anticipated benefits be weighed against possible risks.

Effects on ability to drive and use machines

Methyldopa may cause sedation, usually transient, during the initial period of therapy or whenever the dose is increased. If affected, patients should not carry out activities where alertness is necessary, such as driving a car or operating machinery.

Undesirable effects

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. If affected, patients should not attempt to drive, or operate machinery. Headache, asthenia or weakness may be noted as early and transient symptoms.

The following convention has been utilized for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table MD-38. Tabulated List of Adverse Reactions from Methyldopa

SYSTEM ORGAN CLASS	ADVERSE EVENT TERM	FREQUENCY
Infections and infestations	Sialoadenitis	Not known
Blood and lymphatic system disorders	Hemolytic anemia, bone-marrow failure, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia	Not known
Endocrine disorders	Hyperprolactinemia	Not known
Psychiatric disorders	Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido	Not known
Nervous system disorders	Sedation (usually transient), headache, paresthesia, Parkinsonism, VIIth nerve paralysis, choreoathetosis, mental impairment, carotid sinus syndrome, dizziness, symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)	Not known
Cardiac disorders	Bradycardia, angina pectoris, myocarditis, pericarditis, atrioventricular block	Not known
Vascular disorders	Orthostatic hypotension (decrease daily dosage)	Not known
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Not known
Gastrointestinal disorders	Nausea, vomiting, abdominal distension, constipation, flatulence, diarrhea, colitis, dry mouth, glossodynia, tongue discoloration, pancreatitis	Not known
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Skin and subcutaneous tissue disorders	Rash (eczema, lichenoid eruption), toxic epidermal necrolysis, angioedema, urticaria	Not known
Musculoskeletal and connective tissue disorders	Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia	Not known
Reproductive system and breast disorders	Breast enlargement, gynecomastia, amenorrhea, lactation disorder, erectile dysfunction, ejaculation failure	Not known
General disorder and administration site conditions	Asthenia, oedema (and weigh gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear). Pyrexia	Not known
Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, increased blood urea	Not known

Overdose

Symptoms

Acute overdosage may produce acute hypotension with other responses attributable to brain and gastro-intestinal malfunction (excessive sedation, weakness, bradycardia, dizziness, light-headedness, constipation, distension, flatus, diarrhea, nausea, and vomiting).

Management

If ingestion is recent, emesis may be induced or gastric lavage performed. There is no specific antidote. Methyldopa is dialysable.

Treatment is symptomatic. Infusions may be helpful to promote urinary excretion.

Special attention should be directed towards cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity.

Administration of sympathomimetic agents may be indicated. When chronic overdosage is suspected, methyldopa should be discontinued.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of methyldopa products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on methyldopa tablets.

API

Methyldopa is not included in the WHO PQP. Therefore, there is no WHO-prequalified methyldopa API.

Five manufacturers of methyldopa API (as sesquihydrate) have obtained the certificate of suitability to monographs of the European Pharmacopeia (CEP), confirming its suitable quality for use in medicinal product.

Table MD-39. Manufacturers of Methyldopa API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Methyldopa (monograph number 45)	Zhejiang Chiral Medicine Chemicals Co, Ltd. Hangzhou CN	R1-CEP 2003-241-Rev 03	05/17/2017	Chemistry
Methyldopa (monograph number 45)	Zhejiang Wild Wind Pharmaceutical Co., LTD, Geshan Town CN	R1-CEP 2009-120-Rev 01	04/18/2018	Chemistry
Methyldopa Process B (monograph number 45)	Zhejiang Chiral Medicine Chemicals Co, Ltd. Hangzhou CN	R0-CEP 2018-065-Rev 00	07/09/2018	Chemistry
Methyldopa (monograph number 45)	Egis Pharmaceutical PLC Budapest HU	R1-CEP 1996-033-Rev 07	04/10/2019	Chemistry
Methyldopa (monograph number 45)	Teva Pharmaceutical Industries LTD Tel Aviv – Jaffa IL	R1-CEP 2010-182-Rev 03	03/24/2022	Chemistry
Methyldopa (monograph number 45)	Teva Pharmaceutical Industries LTD Tel Aviv – Jaffa IL	R1-CEP 2010-326-Rev 04	01/05/2022	Chemistry

Other manufacturers of methyldopa API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines[1].

Methyldopa API must meet pharmacopeia specifications such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Note: The Ph.Int., USP and European Pharmacopeia describes methyldopa as sesquihydrate.

Excipients

Excipients must conform to pharmacopeia monographs.

The potential incompatibility of Methyldopa with excipients needs to be considered when selecting the excipients as methyldopa undergoes catalytic oxygenation in the presence of magnesium, cupric, cobalt, nickel and ferric ions.

Additionally, incompatibility was found with reducing carbohydrates. It is recommended to track the Maillard interaction in solid pharmaceutical dosage forms containing lactose as a filler and/or dextrose used as a binder in the granulation and/or as a sweetener in sugar coated solid dosage forms[2].

Manufacturing process

Methyldopa tablets should be manufactured according to recognized principles of GMP using ingredients that comply with specifications designed to ensure the final products meet the requirements of the compendial monographs.

Methyldopa is very hygroscopic and may be sensitive to prolonged exposure to air and light[3]. Therefore, environmental conditions during manufacturing should be defined considering these risks.

Methyldopa has two ortho-phenolic hydroxyl groups in the molecule, which can lead to oxidative discoloration, and is easily oxidized particularly under high-humidity conditions or alkaline conditions. The manufacturing process is usually carried out by direct tableting method or by a granulating and tableting method. To avoid its discoloration and improve stability, the introduction of water in the manufacturing process should be avoided as much as possible, for example through the use of a solvent such as absolute ethyl alcohol. Contact with a metal container during the manufacturing process should also be avoided. Direct compaction would be the best process to avoid presence of water during manufacture. Meanwhile, methods such as film coating or sugar coating are added to increase the stability.

Methyldopa is a fine powder with poor flowability and poor compressibility. Therefore, the formulation should be carefully defined to improve the tableting performance and to avoid oxidative discoloration. It is preferable to use manufacturers that show API with a good flowing index to help with direct compaction. The Hausner ratio must be low.

[1] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.
[2] Siahi, M. R., Rahimi S., Monajjemzadeh F. 2018. "Analytical Investigation of the Possible Chemical Interaction of Methyldopa with Some Reducing Carbohydrates Used as Pharmaceutical Excipients." *Adv Pharm Bull* 8(4): 657-666.
[3] Chemical Datasheet "Methyl dopa" from CAMEO Chemicals version 2.8.0 rev 1. Available at: https://cameochemicals.noaa.gov/chemical/20642

Methyldopa is a film-coated tablet. Film coating or sugar coating are added to increase the stability of the product and prevent the oxidative discoloration of the tablet surface.

The uniformity of the batch used in biowaiver or bioavailability studies should be provided. In addition, a manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In the case where the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three consecutive production scale batches should be submitted.

Notes:

- *The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamines impurity sources include the API, excipients, primary packaging and the manufacturing process.*[4, 5]

Packaging

Methyldopa tablets are usually packed in PVC/PVDC-aluminum foil blister or in glass or plastic bottles.

Suitability of the container should be demonstrated, including:

Safety

- Blister: Declarations as to compliance with appropriate food additive regulations (e.g., US FDA or EU regulations).
- Glass/plastic bottles: food grade declaration and tests as per USP<660>/Ph.Eur. 3.2.1 (Glass); USP<661>/Ph.Eur. 3.1.10 (Plastics).

Protection

- Blister: Water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671> Compatibility.
- Glass/plastic bottles: plastics: WVTR (weight loss) and LT as per USP<671>.

Compatibility

- Accelerated and long-term stability data for the packaged finished products.

Bioequivalence requirements

Methyldopa sesquihydrate is considered as a BCS Class I (High Solubility / High Permeability (HS/HP)) or Class III (High Solubility / Low Permeability (HS/LP)) drug by the WHO.[6] Once

[4] WHO, 2019. "Information Note: Nitrosamine impurities". Available at: https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities

[5] WHO, 2021. "Nitrosamine concerns in rifampicin products – Update". Available at: https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

[6] WHO. 2021. "WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms," Annex 8 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 55th report. Technical Report Series No. 1003. Geneva: WHO.

experimental permeability data are available, the exact class attribution will be possible (i.e. either class I or class III). However, the present solubility characterization is already sufficient to provide an indication that methyldopa sesquihydrate is eligible for biowaiver provided that it meets the following criteria:

BCS Class I criteria:

Comparative in vitro dissolution

- The multisource and the comparator product are similarly rapidly dissolving (as defined below) in standard media at pH 1.2, pH 4.5 and pH 6.8 and meet the criteria of dissolution profile similarity, f2 ≥50 (or equivalent statistical criterion);
- If both the multisource and the comparator products are very rapidly dissolving (as defined below), the two products are deemed equivalent and a profile comparison is not necessary.

Excipients

- It is recommended that the excipients employed in the multisource product be present in the comparator product or be present in other products that contain the same API as the multisource product and that have marketing authorizations in ICH associated countries.
- Critical excipients (e.g., mannitol, sorbitol, surfactants), if present, should not differ qualitatively or quantitatively (i.e. within ± 10.0%) from those of the comparator product.

BCS Class III criteria:

Comparative in vitro dissolution

- Both the multisource and the comparator products are very rapidly dissolving (as defined below) in standard media at pH 1.2, pH 4.5 and pH 6.8

Excipients

- All excipients in the multisource product should be qualitatively the same and quantitatively very similar to that of the comparator product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation.[7]

Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 15 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- ■ pH 1.2 HCl solution or buffer
- ■ pH 4.5 acetate buffer
- ■ pH 6.8 phosphate buffer

Pharmacopeial buffers (e.g., Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media.

Rapidly dissolving

[7] WHO. 2013. "WHO guidelines on variations to a prequalified product." Annex 3 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 47th report. Technical Report Series No. 981. Geneva: WHO.

A multisource product is considered to be rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 30 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Surfactants should not be used in the dissolution media.

An appropriate comparator product is Aldomet® 250 mg Tablets. In all cases, it should be demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g., by effects on gastrointestinal motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

Well established excipients in usual amounts should be used in multisource products. Excipients that might affect the bioavailability of the API (e.g., mannitol, sorbitol, or surfactants, should be identified and an assessment of their impact provided). These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

TRANEXAMIC ACID

INJECTION, 100 MG/ML IN 10-ML AMPOULE

GENERAL PRODUCT INFORMATION

Tranexamic acid is a competitive inhibitor of plasminogen activation. It can reduce bleeding by inhibiting the enzymatic breakdown of fibrinogen and fibrin clots. Tranexamic is relatively cheap in most contexts, easy to administer, and in routine clinical use for reduction of blood loss in surgery and trauma. It is listed on the WHO Essential Medicines List (EML) for the treatment of postpartum hemorrhage (PPH) and for the treatment of adult patients with trauma and significant risk of ongoing hemorrhage.

PPH is the main cause of maternal mortality worldwide. Most of the deaths occur soon after giving birth and almost all (99%) occur in low-income and middle-income countries.[1] The majority of PPH-associated deaths could be avoided by the use of prophylactic uterotonics during the third stage of labor and timely, appropriate management of PPH.

WHO recommends early use of intravenous tranexamic acid within 3 hours of birth in addition to standard care for women with clinically diagnosed PPH following vaginal birth or caesarean section. Tranexamic acid should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.[2]

Tranexamic acid should be recognized as a life-saving intervention and be made readily available at all times in the delivery and postpartum areas of health care facilities for the management of PPH, as part of the standard comprehensive PPH treatment package, including medical (uterotonics), non-surgical, and surgical interventions in accordance with the WHO guidelines.

Tranexamic acid injection should be administered by the intravenous route only. However, obstetricians from several countries have recently reported inadvertent intrathecal administration of

[1] Say, L., Chou, D., Gemmill, A., Tunçalp, Ö., Moller, AB., Daniels, J., Gülmezoglu, AM., Temmerman, M., and Alkema, L. 2014. "Global causes of maternal death: a WHO systematic analysis." *Lancet Glob Health* 2: e323–33. doi: 10.1016/S2214-109X(14)70227-X.

[2] World Health Organization. 2017. WHO recommendation on tranexamic acid for the treatment of postpartum hemorrhage. Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/259374/9789241550154-eng.pdf

tranexamic acid and related serious neurological injuries. In most of the cases reported, tranexamic acid injection was erroneously administered instead of the intended intrathecal anesthetic (e.g., bupivacaine injection) for neuraxial anesthesia.[3,4] WHO and U.S. Food and Drug Administration (FDA) have issued an alert about the risk of inadvertent intrathecal (spinal) administration of tranexamic acid injection.[5,6] This potential risk of medication errors with tranexamic acid injection should be considered and addressed by health care professionals to avoid serious injury or death.

[3] Institute for Safe Medication Practices (ISMP). 2019. Dangerous wrong-route errors with tranexamic acid – A major cause for concern. Available at: https://www.ismp.org/resources/dangerous-wrong-route-errors-tranexamic-acid-major-cause-concern

[4] Patel, S., Robertson, B., McConachie, I. 2019. "Catastrophic drug errors involving tranexamic acid administered during spinal anaesthesia." *Anaesthesia* 74(7): 904-914. doi: 10.1111/anae.14662. Epub 2019 Apr 15. PMID: 30985928.

[5] WHO. 2022. Risk of medication errors with tranexamic acid injection resulting in inadvertent intrathecal injection. Available at: https://www.who.int/news/item/16-03-2022-risk-of-medication-errors-with-tranexamic-acid-injection-resulting-in-inadvertent-intrathecal-injection

[6] The U.S. Food and Drug Administration. 2020. FDA alerts healthcare professionals about the risk of medication errors with tranexamic acid injection resulting in inadvertent intrathecal (spinal) injection. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-healthcare-professionals-about-risk-medication-errors-tranexamic-acid-injection-resulting

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.

2. Procurers need to focus on product quality to ensure the product is sterile and safe for patient use as tranexamic acid is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Tranexamic acid injection products must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

The container-closure system (ampoule) must be sufficient to preserve sterility during the shelf life of the product.

Procurement of 100 mg/mL in 10-mL ampoule presentation is recommended, as per the WHO EML.

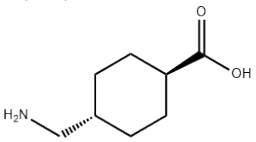
Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Tranexamic acid must be stored safely to ensure that ampoules do not break or leak, which would compromise their sterility. Products are stable at room temperature and do not need to be maintained in the cold chain.

In clinical facilities, tranexamic acid is frequently stored in close proximity with other medicines, including injectable local anesthetics indicated for spinal analgesia (e.g., for caesarean section). The presentation of some of the local anesthetics is similar to the tranexamic acid injection presentation (transparent ampoule containing transparent solution). As a result, tranexamic acid injection can erroneously be administered by intrathecal route, resulting in serious life-threatening injuries, including seizures, cardiac arrhythmias, paraplegia, permanent neurological injury, and death. Health care professionals should therefore consider the following steps as recommended by the US FDA to prevent tranexamic acid injection medication errors:

- Store tranexamic acid injection separately from other drugs, in a way that makes the labels visible to avoid reliance on identifying drugs by the packaging appearance.
- Add an auxiliary warning label to note that it contains tranexamic acid and to be administered by intravenous administration on all tranexamic acid container labels.
- Check the container label to ensure the correct product is selected and administered.
- Use barcode scanning when stocking medication cabinets and preparing or administering the product.

Name of the Medicinal Product	Tranexamic acid injection
Chemical Name	Tranexamic acid (trans-4-(Aminomethyl)cyclohexanecarboxylic acid)
Chemical Structure	$C_8H_{15}NO_2$ 
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Tranexamic acid injection is a sterile solution of tranexamic acid in water for injection. It contains 100 mg of tranexamic acid per mL. The typical excipient is water for injection.[7] However, some formulations may also contain Hydrochloric acid and/or Sodium Hydroxide for pH adjustment.
Packaging and Presentation	The WHO EML recommends tranexamic acid injection 100 mg/mL in 10-mL ampoule.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of June 2022, there has been no tranexamic acid injection prequalified by the WHO PQP. It is recommended to check the updated information at the time of procurement, by going to https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

[7] Based on the formulation of an innovator product, Cyklokapron®.

SRA-approved products

Table T-40. Examples of SRA-Approved Tranexamic Acid Injection 100 mg/mL in 10-mL ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Tranexamic acid 100 mg/mL solution for injection	UK MHRA	Accord Healthcare Ltd, UK	PL 20075/0451	Type I glass 10-mL ampoule	2 years	This medicinal product does not require any special storage conditions.
Tranexamic Acid 100 mg/mL solution for injection/ infusion	UK MHRA	Ibigen S.r.l., Italy	PL 31745/0028	Type I glass 10-mL ampoule	3 years	Do not refrigerate or freeze.
Tranexamic Acid 100 mg/mL solution for injection	UK MHRA	Milpharm Ltd, UK	PL 16363/0476	Type I glass 10-mL ampoule	3 years	This medicinal product does not require any special storage conditions.
Tranexamic acid 100 mg/mL solution for injection/ infusion	UK MHRA	Stargen UK Ltd, UK	PL 21844/0031	Type I glass 10-mL ampoule	3 years	This medicinal product does not require any special storage conditions.
Cyklokapron® injection 100 mg/mL	US FDA	Pfizer, USA	NDA #019281	10-mL single-dose glass ampoule	Not specified	Store at 20°C to 25°C; excursions permitted to 15°C to 30°C [see USP Controlled Room Temperature].
Cyklokapron® tranexamic acid 1000 mg/10 mL solution for injection ampoule	TGA Australia	Pfizer Australia Pty Ltd, Australia	AUST R 166415	Type I glass 10-mL ampoule	3 years	Store below 25°C. Do not freeze. Protect from light.
				10-mL LDPE ampoule	2 years	
Tranexamic-AFT tranexamic acid 1000 mg/10 mL solution for injection ampoule	TGA Australia	AFT Pharmaceuticals Pty Ltd, Australia	AUST R 228945	Type I glass 10-mL ampoule	2 years	Store below 25°C. Do not freeze. Protect from light.
TRANEXAMIC ACID JUNO tranexamic acid 1000 mg/10 mL solution for injection ampoule	TGA Australia	Juno Pharmaceuticals Pty Ltd, Australia	AUST R 222348	Type I glass 10-mL ampoule	2 years	Store below 25°C. Do not freeze. Protect from light.

Note: Many of the Tranexamic acid injection 100 mg/mL that are approved by the US FDA (e.g. those supplied by Fresenius Kabi, Mylan, Exela Pharma, etc) are not included in the list above, as they are available in glass vials of 10 mL different from the presentations recommended by the WHO.

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may change over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross-check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/medicinal-products/union-register/member-states-registers-nationally-authorised-medicinal-products_en
- Swissmedic: https://www.swissmedicinfo.ch/ https://www.swissmedicinfo.ch/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other presentations of tranexamic acid injection on the market include:

- Tranexamic acid injection 100 mg/mL in 5-mL ampoule
- Tranexamic acid injection 100 mg/mL in 10-mL vial

They are used for the same indications, dosage, and administration. However, it is important to note that the WHO EML recommends tranexamic acid injection 100 mg/mL in 10-mL ampoule for convenient use in the treatment of PPH, which requires an administration of a fixed dose of 1 g in 10 mL intravenously (IV) at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes.[1]

When it is necessary to procure the vial presentation, it is important to ensure that glass vial meets compendial requirements such as USP<660> and USP<1660>, and rubber stopper meets compendial requirements such as USP<381> and USP<87>/<88> and its material composition is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines.

Furthermore, tranexamic acid is also available in the tablet form of 500 mg, but it is indicated for hereditary angioneurotic oedema, short term use in the treatment of hyphemia and in patients with established coagulopathies who are undergoing minor surgery, and menorrhagia.

[1] World Health Organization. 2017. WHO recommendation on tranexamic acid for the treatment of postpartum hemorrhage. Geneva: WHO. Available at https://apps.who.int/iris/bitstream/handle/10665/259374/9789241550154-eng.pdf

STORAGE, STABILITY, AND DEGRADATION

Tranexamic acid injection is stable at room temperature and does not require cold chain storage. It is unlikely to undergo any significant degradation as a result of heat if it is properly manufactured, packaged, sterilized, and sealed.

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze.

Tranexamic acid injection is a very stable product. A study by de Guzman et al.[2] demonstrated that tranexamic acid remained functionally stable when stored for up to 12 weeks at temperatures ranging from –20°C to 50°C, as determined by the ability of tranexamic acid to completely inhibit streptokinase-induced fibrinolysis of the platelet-poor plasma. Furthermore, tranexamic acid remained chemically stable when stored for up to 12 weeks at temperatures from 4°C to 50°C and up to 4 weeks at –20°C as determined by high-performance liquid chromatography (HPLC). However, freezing should be avoided as cracks were observed in the ampoules within 1 week.

Furthermore, Loner et al.[3] reported that tranexamic acid remained stable under fluctuating extreme temperatures (seven days of freeze/thaw or heating cycles) and did not significantly degrade.

Tranexamic acid is not sensitive to light.[4,5,6]

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopeia (USP) and British Pharmacopeia (BP), depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the two pharmacopeias are similar, except the assay, related substances, and/or bacterial endotoxin limits.

[2] de Guzman, R., Polykratis, IA., Sondeen, JL., Darlington, DN., Cap, AP., and Dubick, MA. 2013. "Stability of tranexamic acid after 12-week storage at temperatures from -20°c to 50°c." *Prehosp Emerg Care* 17(3): 394–400. doi: 10.3109/10903127.2013.792891.

[3] Loner, C., Estephan, M., Davis, H., Cushman, J., and Acquisto, N. 2019. "Effect of fluctuating extreme temperatures on tranexamic acid." *Prehospital and Disaster Medicine* 34(3): 340–342. doi:10.1017/S1049023X19004308.

[4] Medicines Evaluation Board. 2015. Public assessment report of Tranexaminezuur Sandoz 100 mg/ml, solution for injection (NL/H/3153/001/DC). Available at https://www.geneesmiddeleninformatiebank.nl/pars/h115236.pdf.

[5] Food and Drug Administration. 2009. Environmental assessment: Application number 22-430. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022430s000ea.pdf

[6] Huang, H., Liu, H., Zhou, H., Liang, Z., Song, D., Zhang, Y., Huang, W., Zhao, X., Wu, B., Ye, G., and Huang, Y. 2019. "Drug-release system of microchannel transport used in minimally invasive surgery for hemostasis." *Drug Des Devel Ther* 13: 881–896. doi: 10.2147/DDDT.S180842.

Table T-41. US Pharmacopeia Specifications for Tranexamic Acid Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) Infrared spectroscopy (IR)	The IR spectra from the sample solution comply with that of the standard solution.	USP<197K>
b) HPLC	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay.	USP<621>
pH	6.5–8.0	USP<791>
Assay	90.0–110.0%	HPLC, USP<621>
Impurities	Any unspecified impurity: Not more than 0.1% Total impurities:* Not more than 0.5%	HPLC, USP<621>
Bacterial endotoxins	Not more than 0.5 USP endotoxin units/mg of tranexamic acid	USP<85>
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

** Excluding process impurities monitored in the drug substance, e.g., Tranexamic acid related compound C ((RS)-4-(Aminomethyl)cyclohex-1-enecarboxylic acid hydrochloride); 4-(Aminomethyl)benzoic acid; cis-4-(Aminomethyl)cyclohexanecarboxylic acid; trans,trans-4,4'-[Iminobis(methylene)]dicyclohexanecarboxylic acid*

Table T-42. British Pharmacopeia Specifications for Tranexamic Acid Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification (IR)	The IR spectra from the sample solution comply with that of the standard solution.	Appendix II A
pH	6.5–8.0	Appendix V L
Assay	95.0–105.0%	HPLC, Appendix III D
Related substances**	Impurity A: Not more than 1% Impurity B: Not more 0.5% Impurity C: Not more than 0.1% Impurity D: Not more than 0.1% Any other impurity: Not more than 0.1% Total impurities: Not more than 2.0%	HPLC, Appendix III D
Bacterial endotoxins	Less than 35 IU/mL	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

** *Impurity A = (1r,4r,1'r,4'r)-4,4'-[azanediylbis(methylene)]di(cyclohexane-1-carboxylic acid)*
Impurity B = (1s,4s)-4-(aminomethyl)cyclohexane-1-carboxylic acid
Impurity C = (4RS)-4-(aminomethyl)cyclohex-1-ene-1-carboxylic acid
Impurity D = 4-(aminomethyl)benzoic acid

TRANEXAMIC ACID ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

- Treatment of PPH
- Treatment of adult patients with trauma and significant risk of ongoing hemorrhage

Posology, method, and duration of administration

Treatment of PPH

Use tranexamic acid injection within 3 hours and as early as possible after onset of PPH. Do not initiate tranexamic acid more than 3 hours after birth, unless being used for bleeding that restarts within 24 hours of completing the first dose.

Tranexamic acid should be administered at a fixed dose of 1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose.

Tranexamic acid should be administered slowly as an IV injection over 10 minutes, since bolus injection carries a potential risk of transient lowering of blood pressure.

Treatment of adult patients with trauma and significant risk of ongoing hemorrhage

Standard treatment of local fibrinolysis: 0.5 g (5 mL) to 1 g (10 mL) tranexamic acid by slow intravenous injection or infusion (= 1 mL/minute) two to three times daily.

Standard treatment of general fibrinolysis: 1 g (10 mL) tranexamic acid by slow intravenous injection or infusion (= 1 mL/minute) every 6 to 8 hours, equivalent to 15 mg/kg body weight (BW).

Renal impairment: In renal insufficiency leading to a risk of accumulation, the use of tranexamic acid is contraindicated in patients with severe renal impairment (see also "Contraindications" section below). For patients with mild to moderate renal impairment, the dosage of tranexamic acid should be reduced according to the serum creatinine level:

Table T-43. Tranexamic Acid Dosage for Patients with Mild to Moderate Renal Impairment

SERUM CREATININE (MICROMOL/L)	MG/10 ML	DOSE IV	ADMINISTRATION
120 to 249	1.35 to 2.82	10 mg/kg BW	Every 12 hours
250 to 500	2.82 to 5.65	10 mg/kg BW	Every 24 hours
> 500	> 5.65	5 mg/kg BW	Every 24 hours

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment.

Health care professionals should administer tranexamic acid injection by the intravenous route only. There have been reports of tranexamic acid being mistaken for obstetric spinal anesthesia used for caesarean deliveries resulting in inadvertent intrathecal administration, which may cause serious undesirable adverse effects. Therefore, careful handling of tranexamic acid injection is necessary to prevent medication errors.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the product
- Acute venous or arterial thrombosis (see "Special warnings and precautions for use" section below)
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding (see "Special warnings and precautions for use" section below)
- Severe renal impairment (risk of accumulation)
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)

Special warnings and precautions for use

The indications and method of administration indicated above should be followed strictly:

- Intravenous injections or infusions should be given very slowly (maximum 1 mL per minute);
- Tranexamic acid should not be administered by the intramuscular route.

Convulsions

Cases of convulsions have been reported in association with tranexamic acid treatment. In coronary artery bypass graft (CABG) surgery, most of these cases were reported following IV injection of tranexamic acid in high doses. With the use of the recommended lower doses of tranexamic acid, the incidence of post-operative seizures was the same as that in untreated patients.

Visual disturbances

Attention should be paid to possible visual disturbances including visual impairment, vision blurred, impaired color vision and if necessary, the treatment should be discontinued. With continuous long-term use of tranexamic acid, regular ophthalmologic examinations (eye examinations including visual acuity, color vision, fundus, visual field etc.) are indicated. With pathological ophthalmic changes, particularly with diseases of the retina, the physician must decide after consulting a specialist on the necessity for the long-term use of tranexamic acid in each individual case.

Hematuria

In case of hematuria from the upper urinary tract, there is a risk for urethral obstruction.

Thromboembolic events

Before use of tranexamic acid, risk factors of thromboembolic disease should be considered. In patients with a history of thromboembolic diseases or in those with increased incidence of thromboembolic events in their family history (patients with a high risk of thrombophilia), tranexamic acid should only be administered if there is a strong medical indication after consulting a

physician experienced in hemostaseology and under strict medical supervision (see "Contraindications" section above).

Tranexamic acid should be administered with care in patients receiving oral contraceptives because of the increased risk of thrombosis (see "Interaction with other medicinal products and other forms of interaction" section below).

Disseminated intravascular coagulation

Patients with disseminated intravascular coagulation (DIC) should in most cases not be treated with tranexamic acid (see "Contraindications" section above). If tranexamic acid is given it must be restricted to those in whom there is predominant activation of the fibrinolytic system with acute severe bleeding. Characteristically, the hematological profile approximates to the following: reduced euglobulin clot lysis time; prolonged prothrombin time; reduced plasma levels of fibrinogen, factors V and VIII, plasminogen fibrinolysin and alpha-2 macroglobulin; normal plasma levels of P and P complex, i.e. factors II (prothrombin), VIII and X; increased plasma levels of fibrinogen degradation products; a normal platelet count. The foregoing presumes that the underlying disease state does not of itself modify the various elements in this profile. In such acute cases a single dose of 1 g tranexamic acid is frequently sufficient to control bleeding. Administration of tranexamic acid in DIC should be considered only when appropriate hematological laboratory facilities and expertise are available.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field.

Medicinal products that act on hemostasis should be given with caution to patients treated with tranexamic acid. There is a theoretical risk of increased thrombus-formation potential, such as with estrogens. Alternatively, the antifibrinolytic action of the drug may be antagonized with thrombolytic drugs.

Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

There are no or limited amount of data from the use of tranexamic acid in pregnant women. As a result, although studies in animals do not indicate teratogenic effects, as precaution for use, tranexamic acid is not recommended during the first trimester of pregnancy.

Limited clinical data on the use of tranexamic acid in different clinical hemorrhagic settings during the second and third trimesters did not identify deleterious effect for the fetus.

Tranexamic acid should be used throughout pregnancy only if the expected benefit justifies the potential risk.

Breastfeeding

Tranexamic acid is excreted in human milk. Therefore, breastfeeding is not recommended.

Fertility

There are no clinical data on the effects of tranexamic acid on fertility.

Effects on ability to drive and use machines

No studies have been performed on the ability to drive and use machines.

Undesirable effects

The ADRs reported from clinical studies and post-marketing experience are listed below according to system organ class.

Table T-44. Tabulated List of Adverse Reactions from Tranexamic Acid

SYSTEM ORGAN CLASS	COMMON ≥ 1/100 TO < 1/10	UNCOMMON ≥ 1/1,000 TO < 1/100	FREQUENCY NOT KNOWN (CANNOT BE ESTIMATED FROM THE AVAILABLE DATA)
Immune system disorders			Hypersensitivity reactions including anaphylaxis
Nervous System Disorders			Convulsions particularly in case of misuse (see "Contraindications" and "Special warnings and precautions for use" sections above)
Eye disorders			Visual disturbances including impaired color vision
Vascular disorders			Malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration) Arterial or venous thrombosis at any sites
Gastrointestinal Disorders	Diarrhea Vomiting Nausea		
Skin and subcutaneous tissue disorders		Dermatitis allergic	

Overdose

No case of overdose has been reported.

Signs and symptoms may include dizziness, headache, hypotension, and convulsions. It has been shown that convulsions tend to occur at higher frequency with increasing dose. Management of overdose should be supportive.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of tranexamic acid injection products. When assessing the complete quality/chemical, manufacturing and control (CMC) documentation, assessors should consider the following particular information on tranexamic acid injection.

API

As of June 2022, no tranexamic acid API is prequalified by the WHO PQP.
There are five manufacturers of tranexamic acid API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Table T-45. Manufacturers of Tranexamic Acid API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Tranexamic acid (monograph number 875)	Shilpa Medicate Ltd. Raichur, India	R0-CEP 2018-048-Rev 00	8/8/2019	Chemistry
Tranexamic acid (monograph number 875)	Kyowa Pharma Chemical Co., Ltd. Takaoka, Japan	R1-CEP 2012-271-Rev 01	4/30/2020	Chemistry
Tranexamic acid (monograph number 875)	Asahi Kasei Finechem Co., Ltd. Osaka, Japan	R1-CEP 2008-186-Rev 01	5/5/2020	Chemistry
Tranexamic acid (monograph number 875)	Hunan Dongting Pharmaceutical Co., Ltd. Changde, China	R1-CEP 2006-142-Rev 02	8/27/2020	Chemistry
Tranexamic acid (monograph number 875)	Ami Lifesciences Private Ltd. Karakhadi, India	R0-CEP 2019-250-Rev 02	4/4/2022	Chemistry

Other manufacturers of tranexamic API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

The specifications of tranexamic API should be in line with a pharmacopeial monograph (Ph.Eur./BP or USP), with additional tests/limits for residual solvents and bacterial endotoxins. If intended for use

[1] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 46th report. Technical Report Series No. 970. Geneva: WHO.

in the aseptic manufacture of tranexamic acid injection without a further appropriate sterilization procedure, it must comply with the test for sterility.

Tranexamic acid is hygroscopic. It should be kept in tight containers, and store at a temperature not exceeding 30°C or if sterile, in a sterile, airtight, tamper-evident container.

Excipients

The typical excipient of tranexamic acid injection is water for injection.[2] However, some formulations may also contain Hydrochloric acid and/or Sodium Hydroxide for pH adjustment.

There are no special concerns on the excipients. No excipient with the risk of transmitting TSE/BSE is used.

Manufacturing process

Tranexamic acid injection is a straightforward product to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.
The manufacturing process of tranexamic acid injection is a standard process, which is conducted under appropriate aseptic conditions, including the steps of preparation of the solution (with pH adjustment if necessary), filtration and filling and sealing of the ampoules. Finally, steam sterilization by autoclaving of the filled ampoules is performed. The headspace of the ampoules should be replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

For the sterilization process using an autoclave, details such as F0 range, temperature range and peak dwell time for the FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Neutral type I glass ampoule should be used.

Suitability of container should be demonstrated, including the following properties:

[2] Based on the formulation of an innovator product, Cyklokapron®.

Safety

- The material must meet compendial requirements such as USP<660> and USP<1660>. Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of the product manufacture

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Cyklokapron® (tranexamic acid 100 mg/mL injection, Pharmacia and UpJohn Co/Pfizer). The composition of the proposed product should be the same as the comparator product.

GENTAMICIN

INJECTION, 10 MG/ML IN 2 ML VIAL (AS SULFATE) AND 40 MG/ML IN 2 ML VIAL (AS SULFATE)

GENERAL PRODUCT INFORMATION

Gentamicin injection is recommended by WHO for the treatment of neonatal meningitis and also for severe community acquired bacterial pneumonia in children (co-prescribed with amoxicillin, ampicillin or benzylpenicillin), severe or mild-moderate peritonitis (co-prescribed with ampicillin), severe or mild-moderate peritonial abscess (co-prescribed with ampicillin), complicated severe acute malnutrition in infants, children or adolescents (co-prescribed with ampicillin or benzylpenicillin), and sepsis without septic shock (co-prescribed with amoxicillin, ampicillin or benzylpenicillin). Gentamicin injection is the recommended by WHO for the treatment of gonococcal infection following treatment failure of other antibiotics and for other specified prophylactic measures. It is also considered an essential medicine for child health by the UN Commission on Life-Saving Commodities.

Gentamicin for injection is presented as an aqueous solution of gentamicin sulfate, mostly available in 2-mL vials or ampoules in two concentrations (10 mg/mL or 40 mg/mL). Gentamicin is also available in eye drops for ophthalmological infections, in ear drops for ear infections, and as a topical ointment for skin infections.

The scope of this manual includes only the presentation described in the WHO Essential Medicines List for Children (EMLc) that is gentamicin injection 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers whose gentamicin injection has been approved by an SRA or accepted by the United Nations Children's Fund (UNICEF), and those with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is safe for patient use.

3. Cases of adverse drug reactions (ADRs) relating to gentamicin-containing solutions for injections were reported in different countries due to the presence of histamine in the drug product. Investigations have revealed elevated levels of histamine in gentamicin API linked to a fish peptone raw material that is utilized in the fermentation process . Therefore, if the API is obtained by fermentation, the drug substance and drug product manufacturers need to ensure the appropriate control of the raw materials as part of their auditing strategy. Additionally, the following considerations should be considered:

   - The source of peptone used (e.g. animal or vegetable origin) should be clearly declared by the API manufacturer.
   - If fish peptone is used in the manufacture of the active substance, histamine should be specified and controlled for as an impurity in the specifications.

KEY QUALITY CONSIDERATIONS

Product specification

The product must comply with the quality specifications as detailed in the Annex.

Packaging and labeling

Gentamicin injection should be procured in vial presentations as per the WHO EMLc recommendation of 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial. For typical neonatal dosages, approximately two doses could be obtained from a 10-mg/mL vial and up to eight doses from a 40 mg/mL vial. Note that some SRA-approved products may be presented in ampoules. For ampoules, any medicine not immediately used would have to be discarded, as it cannot be resealed.

The container-closure system (vial and rubber stopper) must be sufficient to preserve sterility during the shelf life of the product.

While pediatric ampoules exist for the intramuscular injections to newborns, the volumes are smaller if the 80 mg/2 ml ampoule is used (it is less painful for the patient). In this situation, syringes and needles of the right sizes for newborns should be considered in the procurement.

Note: Due to the calculations needed to determine the dose volume by weight of the infant, health workers at the primary care level may have difficulty accurately determining the correct amount of drug they should administer. A custom-marked syringe would be best, as a 1-mL syringe with 0.2 increment markings is most relevant for gentamicin administration, so it may be that a regularly marked 1-mL syringe can be used effectively by health care workers for this purpose. Based on a literature review, the syringe specifications shown in the table below are optimal for IM delivery of gentamicin in neonates[1].

ITEM	OPTIMAL RANGE
Gauge	22–25 G
Needle length	16–25 mm
Gradations	< 0.1 mL
Volume	≥1 mL

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify with manufacturers that there are satisfactory stability data to support shelf life and storage conditions.

Gentamicin injection does not need to be maintained in the cold chain, but should be stored below 25°C.

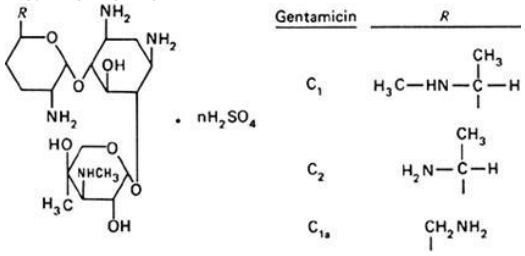
Procurers must ensure that the product is stored safely so that the vial cannot break or leak, which would compromise its sterility.

Additional information about the gentamicin finished product storage requirement can be found in the "Storage, Stability and Degradation" section.

Other considerations

Gentamicin injection must be manufactured in a sterile facility.

[1] Viability of customized, marked syringes for gentamicin delivery for the outpatient treatment of neonatal sepsis. Available at http://www.path.org/publications/files/PATH_dt_cust_syringe_br.pdf

Name of the Medicinal Product	Gentamicin injection
Chemical Name	Gentamicin sulfate Gentamicin sulfate is the sulfate salt of gentamicin fractions C_1, C_2, and C_{1a} produced by the growth of *Micromonospora purpurea*.
Chemical Structure	$C_{60}H_{125}N_{15}O_{25}S$ 
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Gentamicin injection is a sterile solution of gentamicin sulfate in water for injection. – Gentamicin injection 10 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 20 mg of gentamicin base. – Gentamicin injection 40 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 80 mg of gentamicin base. List of typical excipients[2]: – Sodium chloride – Water for injection – Sulfuric acid and/or sodium hydroxide, for pH adjustment Some formulations may contain the following excipients: – Methylparaben (preservative) – Propylparaben (preservative) – Sodium metabisulfite (antioxidant) – Edetate disodium (chelating agent)
Packaging and Presentation	The WHO EMLc includes two presentations for gentamicin injections: 10 mg/mL and 40 mg/mL in 2-mL vials. However, some manufacturers sell it packaged in glass ampoules.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

Gentamicin is not included in the WHO PQP. Therefore, no WHO-prequalified gentamicin products are available.

[2] Based on the formulation of an innovator product, Cidomycin®.

SRA-approved products

As of June 2022, few products are SRA-approved product for Gentamicin sulfate, as shown in table G-1.

Table G-46. Examples of SRA-Approved Gentamicin Injection 10 mg; 40 mg (as sulfate)/mL in 2-mL Vial or Ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Gentamicin sulfate EQ 40 mg base/mL EQ 10 mg base/mL	US FDA	Fresenius Kabi, USA	ANDA #062366	10 mg/mL: single-dose vials; 2 mL 40 mg/mL: multiple-dose flip-top vials; 2 mL	Not specified	Store at 20–25˚C. [See USP, Controlled room temperature.]
Gentamicin sulfate EQ 40 mg base/mL EQ 10 mg base/mL	US FDA	Hospira, USA	ANDA #062420	Single-dose flip-top vials; 2 mL	Not specified	Store at 20–25˚C. [See USP, Controlled room temperature.]
Cidomycin® 80 mg/2 mL solution for injection	UK MHRA	Aventis Pharma (Sanofi-Aventis) Ltd, UK	PL 04425/0672	Colorless glass ampoules (type I) or colorless glass vials (type I) closed with chlorobutyl rubber stopper sealed with an aluminum capsule	3 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin 10 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, UK	PL 29831/0659	Type I glass ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.
Gentamicin 40 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, UK	PL 29831/0660	Type I glass ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.
Gentamicin 40 mg/mL injection	UK MHRA	Hospira UK Ltd,	PL 04515/0037	Clear, type I glass vials; 2 mL	3 years	Do not store above 25°C.
Gentamicin 40 mg/mL solution for injection	UK MHRA	Amdipharm UK	PL 20072/0056	Colorless, type I glass ampoules; 2 mL	4 years	Do not store above 25°C. Do not freeze.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Gentamicin pediatric 20 mg/2 mL solution for injection	UK MHRA	Ennogen Pharma Ltd, UK	PL 40147/0042	Clear glass ampoules; 2 mL	2 years	Store below 25°C. Protect from light.
Gentamicin pediatric 20 mg/2 mL solution for injection	UK MHRA	Zentiva Pharma UK Ltd, UK	PL 17780/0507	Vials; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin 40 mg / mL Solution for injection / infusion	UK MHRA	Noridem Enterprises Limited Cyprus	PL 24598/0069	Type I, clear glass ampoules; 2 mL	3 years	This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.
Gentamicin 40 mg / mL Solution for injection / infusion	UK MHRA	Panpharma France	PL 44124/0028	Colorless ampoules (glass type I); 2 mL	3 years	Store below 30°C.
Gentamicin 40 mg / mL Solution for injection / infusion	UK MHRA	Panpharma UK	PL 44789/0001	Colorless ampoules (glass type I); 2 mL	3 years	Store below 30°C.
Gentamicin injection USP 10 mg/mL	Health Canada	Hikma Canada Limited, Canada	02470462	Single-use ampoules; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection USP 40 mg/mL	Health Canada	Hikma Canada Limited, Canada	02457008	Single-use ampoules; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection USP 10 mg/mL	Health Canada	Sandoz Canada Incorporated	02242652	Single-use vials; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection USP 40 mg/mL	Health Canada	Sandoz Canada Incorporated	02268531	Single-use vials; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection BP 80 mg/2 mL	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 11376	LDPE ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.
DBL Gentamicin 10mg/1mL(as sulfate) Injection	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 16339	Ampoule; 2 mL	3 years	Store below 25 degrees Celsius
Hospira Gentamicin Injection BP 80 mg/2 mL vial	TGA (Australia)	Hospira Australia Pty Ltd, Australia	AUST R 34197	Glass Type I Clear vials; 2 mL	36 months	Store below 25°C.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
DBL Gentamicin 80mg/2mL Injection BP	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 47268	Ampoule; 2 mL	3 years	Store below 25°C.
Gentamicin 80 mg/2 mL Injection BP	TGA (Australia)	Pfizer (Perth) Pty Ltd	AUST R 278535	LDPE ampoules; 2 mL	2 years	Store below 25°C. Protect from light.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP (including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information) will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may crosscheck the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other formulations of gentamicin that exist in the market include the following products.

- Gentamicin 1 mg/mL solution for injection
- Gentamicin 3 mg/mL solution for infusion
- Gentamicin eye/ear drops 0.3% w/v
- Gentamicin intrathecal 5 mg/mL solution for injection
- Implants—each chain consists of 10, 30, or 60 beads (each bead contains 7.5 mg gentamicin sulfate)
- Gentamicin 0.3% w/v and hydrocortisone acetate 1% w/v ear drops
- Gentamicin 1 mg (as 1.67 mg gentamicin sulfate) and betamethasone 0.5 mg (as 0.64 mg betamethasone dipropionate) cream

It is important to note that the WHO EMLc recommends gentamicin injection 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial for the treatment of community-acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children. Therefore, the procurement agency must focus on procurement of those presentations as per the WHO EML.

STORAGE, STABILITY, AND DEGRADATION

Gentamicin injection is stable at room temperature and does not require cold chain storage.

Shelf life: 2–4 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage conditions: Do not store above 25°C. Do not refrigerate or freeze. Protect from light.

The shelf life and storage condition of each SRA-approved product can be found in Table G-1.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopoeia and British Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the two pharmacopoeias are similar, except the assay limits and the composition of gentamicin sulfate (required only in the BP).

Table G-47. US Pharmacopeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter.	Visual inspection
Identification (TLC)	The intensities and Rf values of the three principal spots obtained from the test solution correspond to those obtained from the standard solution.	USP<621>
pH	3.0–5.5	USP<791>
Assay	90.0–125.0%	USP<81>
Bacterial endotoxins	Not more than 0.71 USP endotoxin unit/mg of gentamicin	USP<85>
Particulate matter	Meet the requirements for small-volume injections	USP<788>
Extractable volume	Comply	USP<1>
Sterility	Sterile	USP<71>

Table G-48. British Pharmacopeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter.	Visual inspection
Identification a) TLC	The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).	Appendix III A
Identification b) Liquid chromatography	The retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).	Appendix III D
pH	3.0–5.5	Appendix V L
Assay	The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. Calculate the content of gentamicin in the injection taking each 1,000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated content.	Appendix XIV A
Composition of gentamicin sulfate (liquid chromatography)	The proportions are within the following limits: C1 25.0–50.0% C1a' 10.0–35.0% C2 plus C2a' 25.0–55.0%	Appendix III D
Bacterial endotoxins	Below 7.1 IU per mL	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

GENTAMICIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Gentamicin is an aminoglycoside antibiotic used in the treatment of various bacterial infections. It is recommended by WHO for the treatment of neonatal meningitis and also for severe community acquired bacterial pneumonia (co-prescribed with amoxicillin, ampicillin or benzylpenicillin), severe or mild-moderate peritonitis (co-prescribed with ampicillin or benzylpenicillin), severe or mild-moderate peritoneal abscess (co-prescribed que ampicillin), complicated severe acute malnutrition in infants, children or adolescents (co-prescribed with ampicillin), and sepsis without septic shock (co-prescribed with amoxicillin, ampicillin or benzylpenicillin). Gentamicin injection is the second-line drug recommended by WHO for the treatment of gonococcal infection and for other specified prophylactic measures.

Posology, method, and duration of administration[1,2]

Severe cases of community-acquired pneumonia in children

- Neonates: gentamicin (IV/IM) 5 mg/kg dose given once a day, with ampicillin (IV/IM) 50 mg/kg dose given every 12 hours (1st week of life) or every 8 hours (>1st week of life), for 5 days (consider longer treatment if the patient is not clinically stable at day 5). Ampicillin can be replaced by amoxicillin (IV/IM) 50 mg/kg dose given every 12 hours (1st week of life) or every 8 hours (>1st week of life). Ampicillin can be also replaced by benzylpenicillin (IV) 50.000 IU/kg (30 mg/kg) given every 8 hours.
- Children: gentamicin (IV/IM) 7.5 mg/kg dose given once a day with ampicillin (IV/IM) 50 mg/kg dose given every 8 hours for 5 days (consider longer treatment if the patient is not clinically stable at day 5). Ampicillin can be replaced by amoxicillin (IV/IM) 50 mg/kg dose given every 8 hours. Ampicillin can be also replaced by benzylpenicillin (IV) 50.000 IU/kg (30 mg/kg) given every 8 hours.
- If no clinical response to ampicillin and gentamicin after 48-72 hours, change to second line treatment with cefotaxime (IV/IM) 50mg/kg dose given every 8 hours or ceftriaxone (IV/IM) 80 mg/kg dose given once a day.
- If HIV-positive and greater than 1 month of age (Pneumocystis jirovecii pneumonia is a risk), add empiric sulfamethoxazole + trimethoprim: 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole, given every 8 hours for 3 weeks.
- Severe pneumonia in school age children, may be caused by *Mycoplasma pneumoniae* (rare occurrence), which is unresponsive to beta-lactams. In this case, macrolides (e.g. clarithromycin) are options for treatment.

Community-acquired sepsis of bacterial origin in neonates and children

- Hospitalized patients

[1] WHO Essential Medicines List Antibiotic Book – Infographics. Draft for public comment. Version 1.1 (Nov 15, 2021).
[2] The WHO Essential Medicines List Antibiotic Book – Draft for public comment. November 18, 2021.

- Neonates: gentamicin (IV) 5 mg/kg dose given once a day, with ampicillin (IV) 50 mg/kg dose given every 12 hours (1st week of life) or every 8 hours (>1st week of life), for 7 days (14 days in case of meningitis). Ampicillin can be replaced by benzylpenicillin (IV) 50.000 IU/kg dose (30 mg/kg dose) given every 8 hours.
- Children: gentamicin (IV) 7.5 mg/kg dose given once a day with ampicillin (IV) 50 mg/kg dose given every 12 hours (1st week of life) or given every 8 hours (>1st week of life) for 7 days (14 days in case of meningitis). Ampicillin can be replaced by benzylpenicillin (IV) 50.000 IU/kg/dose (30 mg/kg dose) given every 8 hours.

■ Referral to hospital not possible
  - Neonates:
    Gentamicin (IM) 5 mg/kg dose given once a day, with amoxicillin (oral) 50 mg/kg dose given every 12 hours, for 7 days (14 days in case of meningitis).

    Consider giving ampicillin and gentamicin prophylactically for 2 days if there are significant risk factors for infection as follows:

    – Membranes ruptured > 18 hours before delivery
    – Mother had fever > 38°C before delivery or during labor
    – Amniotic fluid was foul smelling or purulent

  - Children:
    Gentamicin (IM) 7.5 mg/kg dose given once a day, with amoxicillin (oral) 50 mg/kg dose given every 12 hours, for 7 days (14 days in case of meningitis).

Community-acquired sepsis of bacterial origin in adults

Clinical sepsis of unknown origin

■ Gentamicin (IV) 5 mg/kg given once a day, with ceftriaxone (IV) 2 g given once a day or cefotaxime (IV) 2 g given every 8 hours, for 7 days (but duration depends on the patient's underlying disease, the causative pathogen (if any identified later on) and clinical progression).

  In case of meningitis the treatment should be given for 10 days (may differ in epidemics and with different pathogens). For lower respiratory tract infections, the treatment should be provided for 5 days.

  Gentamicin retains activity against ESBL-producing strains and can be considered as a carbapenem-sparing option.

Bacterial meningitis in neonates (< 2 months)

■ 1st week of life: gentamicin (IV) 5 mg/kg given once a day, with ampicillin (IV) 50 mg/kg dose given every 12 hours. Ampicillin can be replaced by ceftriaxone (IV) 100 mg/kg given once a day, or by cefotaxime (IV) 50mg/kg dose given every 12 hours.

■ > 1st week of life: 7.5 mg/kg given once a day, with ampicillin (IV) 50 mg/kg dose given every 8 hours. Ampicillin can be replaced by ceftriaxone (IV) 100 mg/kg given once a day, or by cefotaxime (IV) 50mg/kg/dose given every 6 hours.

■ Total treatment duration:
  - Unconfirmed pathogen: 3 weeks
  - Confirmed *pneumococcal meningitis*: 10–14 days
  - Confirmed *meningococcal meningitis*: 5–7 days
  - Confirmed *Listeria meningitis*: 21 days

Acute cholecystitis or cholangitis in children

Mild and Severe cases

- Neonates: gentamicin (IV) 5 mg/kg given once daily, with ampicillin (IV) 50 mg/kg dose given every 12 hours (first week of life) or every 8 hours (beyond first week of life), and with metronidazole oral/IV 7.5 mg/kg dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg).
- Children: gentamicin (IV) 7.5 mg/kg given once daily given with ampicillin (IV) 50 mg/kg dose given every 8 hours and with metronidazole oral/IV 7.5 mg/kg dose given every 8 hours. Oral weight bands for metronidazole:
  - 3 < 6 kg: 30 mg given every 8 hours
  - 6 < 10 kg: 50 mg given every 8 hours
  - 10 < 15 kg: 100 mg given every 8 hours
  - 15 < 20 kg: 150 mg given every 8 hours
  - 20 < 30 kg: 200 mg given every 8 hours
  - ≥ 30 kg: use adult dose
- Treatment duration:
  - Acute Cholecystitis:
    - Uncomplicated Cases: Antibiotics can be stopped once gallbladder is removed
    - Complicated Cases: 5 days is adequate in most cases with good clinical recovery and source control
  - Acute Cholangitis:
    - All Cases: Give antibiotics until biliary drainage procedures are performed and continue for a total of 5 days after successful source control

If signs and symptoms persist, abdominal imaging is suggested or an alternative extra-abdominal source of infection should be considered.

Antibiotic treatment for acute appendicitis

Mild and Severe cases

- Neonates: gentamicin (IV) 5 mg/kg given once daily, with ampicillin (IV) 50 mg/kg dose given every 12 hours (first week of life) or every 8 hours (beyond first week of life), and with metronidazole oral/IV 7.5 mg/kg dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg).
- Children: gentamicin (IV) 7.5 mg/kg given once daily, with ampicillin (IV) 50 mg/kg dose given every 8 hours and with metronidazole oral/IV 7.5 mg/kg dose given every 8 hours.
- Treatment duration:
  - Uncomplicated Cases: Antibiotics can be stopped once surgery has been performed and child is well.
  - Complicated Cases: Antibiotics can be continued for a total of 5 days provided that symptoms are resolved, and the source of infection was eliminated with surgery.
  - If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Upper urinary tract infections

Severe cases

- Neonates: gentamicin (IV) 5 mg/kg dose given once a day. It may be prescribed with ceftriaxone (IV/IM) 80 mg/kg dose given once a day or cefotaxime (IV/IM) 50mg/kg dose given every 8 hours.
- Children: gentamicin (IV) 7.5 mg/kg dose given once a day. It may be prescribed with ceftriaxone (IV/IM) 80 mg/kg dose given once a day or cefotaxime (IV/IM) 50mg/kg dose given every 8 hours.

- Adults: gentamicin (IV): 5 mg/kg given once a day. It may be prescribed with ceftriaxone (IV/IM) 1 g given every 24 hours or cefotaxime (IV/IM) 1 g given every 8 hours.
- Treatment duration: clinical improvement is usually evident within 48-72 hours of starting treatment; if signs and symptoms persist, consider and investigate a possible complication (e.g. abscess) and review the results of the urine culture to verify that the pathogen is susceptible to the antibiotic used.

Consider gentamicin or amikacin where ESBL-producing isolates are highly prevalent.

In very sick patients, gentamicin (or amikacin) can be given in combination with ceftriaxone (or cefotaxime).

Antibiotic prophylaxis before surgical procedures

Contaminated procedure (2nd choice):

- Neonates: gentamicin (IV) 5 mg/kg single dose and metronidazole (IV) 7.5 mg/kg single dose.
- Children: gentamicin (IV) 7.5 mg/kg single dose and metronidazole (IV) 7.5 mg/kg single dose.
- Adults: gentamicin (IV) 5 mg/kg single dose and metronidazole (IV) 500 mg single dose.

Gentamicin should be given in combination with metronidazole and not as a stand-alone option in contaminated surgical procedures because, if given alone, it provides insufficient coverage of anaerobic bacteria.

Urologic procedures (2nd choice)

- Neonates: gentamicin (IV) 5 mg/kg single.
- Children: gentamicin (IV) 7.5 mg/kg single dose.
- Adults: gentamicin (IV) 5 mg/kg single dose.

Gonococcal infection

- Retreatment after treatment failure: gentamicin 240 mg IM combined with azithromycin 2 g oral.
- Genital and Anorectal Infections (2nd choice): gentamicin 240 mg IM

The 2021 EML lists gentamicin however, this option is not recommended in the WHO 2016 guidelines. Only use single therapy if local resistance data confirm susceptibility to the antibiotic.

Pyogenic liver abscess

- Severe Cases in neonates: gentamicin (IV) 5 mg/kg every 24 hours, combined with ampicillin (IV) 50mg/kg dose every 12 hours (before first week of life) or every 8 hours (beyond first week of life) and with metronidazole (IV/oral) 7.5 mg/kg dose every 12 hours (for IV loading dose 15 mg/kg).
- Severe Cases: gentamicin (IV) 7.5 mg/kg every 24 hours combined with ampicillin (IV) 50mg/kg dose every 12 hours (before first week of life) or every 8 hours (beyond first week of life) and with metronidazole (IV/oral) 7.5 mg/kg dose given every 8 hours.

For metronidazole:

  - 3 < 6 kg: 30 mg given every 8 hours
  - 6 < 10 kg: 50 mg given every 8 hours

- 10 < 15 kg: 100 mg given every 8 hours
- 15 < 20 kg: 150 mg given every 8 hours
- 20 < 30 kg: 200 mg given every 8 hours
- ≥ 30 kg: use adult dose

- Treatment duration: usually long (at least 4 weeks) depending on adequate source control with drainage procedures. Follow up imaging can help defining antibiotic treatment duration.

Other infections

Adults

- Serious infections: If renal function is not impaired, 5mg/kg/daily in divided doses at 6- or 8-hourly intervals. The total daily dose may be subsequently increased or decreased as clinically indicated.
- Systemic infections: If renal function is not impaired, 3–5 mg/kg/day in divided doses according to severity of infection, adjusting according to clinical response and body weight.
- Urinary tract infections: As for "Systemic infections," above. Or, if renal function is not impaired, 160 mg once daily may be used.

Pediatric patients

- The daily dose recommended in children aged 1 year and above and adolescents with normal renal function, is 3–6 mg/kg body weight per day as 1 dose (preferred) or up to 2 single doses.
- The daily dose in infants after the first month of life is 4.5–7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.
- The daily dose in neonates and preterm infants (aged 0–4 weeks old) is 4–7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

The elderly

- There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity, whether secondary to previous eighth-nerve impairment or to borderline renal dysfunction. Accordingly, therapy should be closely monitored by frequent determination of gentamicin serum levels, assessment of renal function, and signs of ototoxicity.

Renal impairment

- In impaired renal function, the recommended daily dose must be decreased and adjusted according to renal function.
- Gentamicin is excreted by simple glomerular filtration; a reduced dosage is therefore necessary where renal function is impaired.

Contraindications

Hypersensitivity to gentamicin or to any of the excipients, pregnancy, and myasthenia gravis.

Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinine, creatinine clearance), control of function of vestibule and cochlea, and hepatic and laboratory parameters is recommended.

Ototoxicity has been recorded following the use of gentamicin. Groups at special risk include patients with impaired renal function, infants, and possibly the elderly. Consequently, renal, auditory, and vestibular functions, as well as gentamicin serum levels, should be monitored in these patients to avoid peak concentrations above 10 mg/L and troughs above 2 mg/L when administering gentamicin twice daily and 1 mg/L for a once-daily dose. As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery. In some patients with impaired renal function, there has been a transient rise in blood urea nitrogen, which usually reverts to normal during or following cessation of therapy. It is important to adjust the frequency of dosing according to the degree of renal function.

Gentamicin should be used in pregnancy only if considered essential by the physician (see section "Pregnancy and lactation" of this annex).

Gentamicin should be used with care in conditions characterized by muscular weakness.

In cases of significant obesity, gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered.

Interaction with other medicinal products and other forms of interaction

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are believed to enhance the risk of ototoxicity, and amphotericin B, cisplatin and ciclosporin are potential enhancers of nephrotoxicity.

Any potential nephrotoxicity of cephalosporins, and in particular cephaloridine, may also be increased in the presence of gentamicin. Consequently, if this combination is used, monitoring of renal function is advised.

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anesthesia.

Indomethacin possibly increases plasma concentrations of gentamicin in neonates.

Concurrent use with oral anticoagulants may increase the hypothrombinemic effect.

Concurrent use of bisphosphonates may increase the risk of hypocalcemia.

Concurrent use of the botulinum toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.

Pregnancy and lactation

There are no proven cases of intrauterine damage caused by gentamicin. However, in common with most drugs known to cross the placenta, usage in pregnancy should be considered only in life-threatening situations where expected benefits outweigh possible risks. In the absence of gastrointestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

Effects on ability to drive and use machines

Not known.

Undesirable effects

Side effects include vestibular damage or hearing loss, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction. Nephrotoxicity (usually reversible) and acute renal failure, hypersensitivity, anemia, blood dycrasias, purpura, stomatitis, convulsions, and effects on liver function occur occasionally.

Rarely, hypomagnesemia on prolonged therapy and antibiotic–associated colitis have been reported.

Nausea, vomiting, and rash have also been reported.

Central neurotoxicity, including encephalopathy, confusion, lethargy, mental depression, and hallucinations, has been reported in association with gentamicin therapy but is extremely rare.

Peripheral neuropathy: frequency not known.

Overdose

Hemodialysis and peritoneal dialysis will both aid in removing gentamicin from the blood, but the former is probably more efficient. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of gentamicin injection products. When assessing the complete quality/CMC documentation, assessors should particularly consider the following information on gentamicin injection.

API

Gentamicin is not included in the WHO PQP. Therefore, no WHO-prequalified gentamicin API exists.

Only two manufacturers of gentamicin sulfate API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming their suitable quality for use in medicinal products.

Table G-49. Manufacturers of Gentamicin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Gentamicin sulfate (monograph number 331)	LEK Pharmaceuticals D.D. SI 1526 Ljubljana, Slovenia	R1-CEP 2005-121-Rev 01	2/3/2016	Chemica
Gentamicin sulfate (monograph number 331)	Fujian Fukang Pharmaceutical Co, Ltd, CN 350 002 Fuzhou, China	R1-CEP 1998-155-Rev 10	2/18/2019	Chemica

Other manufacturers of gentamicin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines[3].

Gentamicin API must meet pharmacopoeia specifications such as those of the International Pharmacopoeia, European Pharmacopoeia, and US Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Due to the risk of adverse drug reactions (ADRs) from the presence of histamine in gentamicin API, the source of peptone used (e.g. animal or vegetable origin) should be clearly declared by the API manufacturer. If fish peptone is used in the manufacture of the active substance, the histamine should be specified and controlled for as an impurity in the specifications.

[3] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.

Excipients

Gentamicin injection may contain suitable buffers, preservatives, and sequestering agents, unless it is intended for intrathecal use, in which case it contains only suitable tonicity agents.

The typical excipients of gentamicin injection include sodium chloride, water for injection, and sulfuric acid and/or sodium hydroxide, for pH adjustment. There are no special concerns with the excipients. No excipient with the risk of transmitting TSE/BSE is used.

The quality of all excipients should be compliant with recognized pharmacopoeias (Ph.Int., Ph.Eur./BP, or USP).

Some formulations may contain methylparaben and propylparaben as preservatives when the product is intended for multiple-dose use. Where methylparaben and propylparaben are included in the formulation as antimicrobial preservatives, their assays (preservative contents) should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of parabens is below 90.0%, its effectiveness should be established by appropriate studies (e.g., USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP containing a concentration of methylparaben and propylparaben corresponding to the lower proposed acceptance criterion.

Where sodium metabisulfite is included in the formulation as an antioxidant, the effectiveness of the proposed concentration should be justified and verified by appropriate studies.

Manufacturing process

Gentamicin injection is a straightforward drug to manufacture, but the main quality concerns are the sterilization process and the sterility of the facility where it is made.

The manufacturing process of gentamicin injection is a standard process conducted under appropriate aseptic conditions, and includes the steps of preparation of the solution with adjustment of pH, prefiltration and sterile filtration, and filling and sealing of the ampoules. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacturing.

The filters used in sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of absorption of the API or any of the components. The headspace of the vials should be replaced with nitrogen during the filling process to prevent oxidation of the API.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production-scale batches should be submitted.

Notes:

- *The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*

- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[4, 5]

Packaging

Neutral type I glass vials should be used.

Suitability of container should be demonstrated, including the following properties:

Safety

- Glass vials must meet compendial requirements such as USP<660> and USP<1660>.
- Rubber stoppers must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as absorption.
- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously, or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and with the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Cidomycin® (gentamicin injection 80 mg/2 mL solution for injection 40 mg/mL, Sanofi-Aventis), gentamicin sulfate injection 10 mg/mL, 40 mg/mL (Fresenius Kabi, USA), and gentamicin sulfate injection 10 mg/mL, 40 mg/mL (Hospira, USA). The composition of the proposed product should be the same as the comparator product.

[4] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[5] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

7.1% CHLORHEXIDINE DIGLUCONATE

SOLUTION OR GEL

GENERAL PRODUCT INFORMATION

Chlorhexidine (digluconate or gluconate)[1] is a broad-spectrum antiseptic. It has been widely used in a range of applications including wound care, hand washes, preoperative body shower, oral hygiene, and general disinfection.

According to the WHO guideline for umbilical cord care and the WHO guideline for recommendations on maternal and newborn care for a positive postnatal experience, chlorhexidine is recommended to the umbilical cord stump for the prevention of neonatal infection. The applications are for clean, dry umbilical cord care (recommended) and in settings where harmful traditional substances (e.g. animal dung) are commonly used on the umbilical cord, for the daily application of 4% chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) to the umbilical cord stump in the first week after birth (context-specific recommendation).Chlorhexidine is identified by the UN Commission on Life-Saving Commodities for Women and Children as one of 13 lifesaving commodities for women and children. The gel form of 7.1% chlorhexidine digluconate is proven to be as effective as the solution form. Chlorhexidine, both gel and solution, is included in the WHO Model List of Essential Medicines for Children (EMLc) under Specific Medicines for Neonatal Care. This is a higher concentration than the 5% chlorhexidine digluconate (delivering 2.8% chlorhexidine) listed on the EMLc as an antiseptic.

This document focuses on the presentation used for the umbilical cord care according to the WHO EMLc which is 7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine.

[1] It is common practice to use chlorhexidine gluconate and chlorhexidine digluconate interchangeably when referring to the chlorhexidine solution. Chlorhexidine digluconate is used in the European and International Pharmacopeias, while chlorhexidine gluconate is used in the US Pharmacopeia. Chlorhexidine digluconate is used throughout this document for precision and consistency.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procure only 7.1% chlorhexidine digluconate solution or gel for umbilical cord care that is produced by cGMP-compliant pharmaceutical manufacturers. 7.1% chlorhexidine digluconate solution or gel for umbilical cord care is considered a medicine by inclusion in the WHO EML, and therefore, procurement should be based on the product quality.

2. Chlorhexidine that is procured for umbilical cord care should be specifically formulated as topical medicine, which is different in strength from other pharmaceutical and non-pharmaceutical products containing chlorhexidine digluconate, such as presurgical and oral antiseptics, surface disinfectants, and hand sanitizers.

3. The product should not contain alcohol. Topically applied products containing ethanol alcohol may cause percutaneous toxicity in the newborn.

4. Procurers need to focus on product quality to ensure safety for the patient.

5. WHO[2] has issued an alert on multiple recent reports of eye injury, including blindness, with the use of chlorhexidine gluconate 7.1%. This product may cause serious harm if mistakenly applied to the eyes, therefore the following recommendations were provided:

   - Select the optimal primary container/dosage form for chlorhexidine gluconate 7.1% or modify the design of the container to distinguish the product from other medicines typically used for newborns.
   - The product label should be updated with appropriate information on the safe use of the product. More detailed instructions for users (flyers, posters, pictorials etc.) that are culturally appropriate and easy to understand are recommended to avoid misuse of the product.

KEY QUALITY CONSIDERATIONS

Product specification

7.1% chlorhexidine digluconate solution or gel for umbilical cord care products must comply with the quality specifications as detailed in section 4.

Chlorhexidine for umbilical cord care should be procured in a concentration of 7.1% chlorhexidine digluconate, delivering 4% free chlorhexidine. There is common confusion regarding the concentrations of chlorhexidine digluconate versus free chlorhexidine. The conversion between the two is listed in the table below. It is important to note that the WHO EMLc also includes 5%

[2] https://www.who.int/news/item/28-08-2020-chlorhexidine-7-1-digluconate-(chx)-aqueous-solution-or-gel-(10ml)-reports-of-serious-eye-injury-due-to-errors-in-administration

chlorhexidine digluconate as an antiseptic, which delivers only 2.8% free chlorhexidine, a lower level than is recommended for umbilical cord care.

Procurers should be aware of the difference between chlorhexidine digluconate and free chlorhexidine and not misunderstand that the "5% chlorhexidine digluconate" listed on the EMLc for antiseptic is higher or more effective than 4% free chlorhexidine.

Table CD-50: Equivalency of Free Chlorhexidine from Chlorhexidine Digluconate

CHLOROHEXIDINE DIGLUCONATE	EQUIVALENT TO FREE CHLORHEXIDINE	NOTES
20.0%	11.3%	20.0% chlorhexidine digluconate will deliver 11.3% free chlorhexidine. 20% chlorhexidine digluconate is the concentration of API used for manufacture of chlorhexidine topical solution and gel.
7.1%	4.0%	7.1% chlorhexidine digluconate will deliver 4.0% free chlorhexidine. 7.1% chlorhexidine digluconate is the concentration of FPP listed on the EMLc for umbilical cord care.
5.0%	2.8%	5.0% chlorhexidine digluconate will deliver 2.8% free chlorhexidine. 5.0% chlorhexidine digluconate is the concentration of FPP listed on the EMLc for antiseptic.

Only two dosage forms—solution or gel—of 7.1% chlorhexidine digluconate should be procured. Both solution and gel are equally effective for umbilical cord care. Selection of the dosage form (solution or gel) will depend on: which form is most acceptable to mothers, caregivers, skilled providers, and others who are likely to use the product; product availability (e.g., ease of production/import and supply sustainability); and an evaluation of the primary containers for the selected dosage form.

Chlorhexidine digluconate may be available in other concentrations and dosage forms, such as cream or lotion. However, the human body might absorb chlorhexidine gluconate from these dosage forms differently than from the solution or gel forms. In addition, the shelf life and compatibility with other ingredients could be adversely affected when dosage forms are changed.

Procure only a formulation of 7.1% chlorhexidine digluconate that does not contain alcohol. Use of alcohol might cause pain or a burning sensation in newborns. Further, topically applied products containing ethanol alcohol may cause percutaneous toxicity in the newborn. Procurers should ask the product supplier/manufacturer to provide a list of inactive ingredients to ascertain that the product contains no alcohol.

Packaging and labeling

As sunlight adversely affects the stability of chlorhexidine digluconate, transparent primary containers should be avoided.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Additional information about the storage requirements can be found in the "Storage, Stability and Degradation" section.

Name of the Medicinal Product

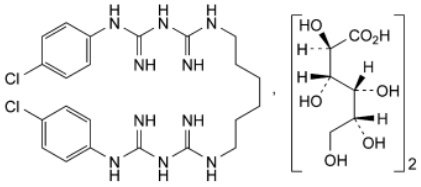
7.1% Chlorhexidine digluconate solution or gel for umbilical cord care

Chemical Name

Chlorhexidine digluconate;
1,1'-(hexamethylene)bis[5-(4-chlorophenyl)biguanide] di-d-gluconate, 1,1'-(hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide] di-d-gluconate

Chemical Structure

$C_{34}H_{54}Cl_2N_{10}O_{14}$
$C_{22}H_{30}Cl_2N_{10}$, $2C_6H_{12}O_7$



Pharmaceutical Form

Topical solution—clear, colorless or pale yellow liquid
Topical gel—colorless to yellow translucent gel

Qualitative and Quantitative Composition

Solution
Chlorhexidine digluconate topical solution is a solution of "chlorhexidine digluconate solution" in a suitable vehicle. It contains chlorhexidine digluconate 7.1% (equivalent to 4% chlorhexidine).

Each 100 mL contains 7.1 g chlorhexidine digluconate equivalent to 4 g chlorhexidine.

List of excipients:
– Purified water
– Sodium hydroxide
– Benzalkonium chloride (optional)

Gel
– Chlorhexidine digluconate topical gel is a solution of chlorhexidine digluconate in a suitable water-miscible basis. It contains chlorhexidine digluconate 7.1% (equivalent to 4% chlorhexidine).
– Each sachet contains a 3-g dose containing 213 mg of chlorhexidine digluconate equivalent to 120 mg chlorhexidine.

Composition[3]:

COMPONENT	QUANTITY (% W/W)
Chlorhexidine digluconate solution, 20% w/v	37.81*
Guar gum	1.40
Sodium acetate trihydrate	0.10
Purified water	QS to 100

** It may be adjusted for potency.*

Packaging and Presentation

The WHO EMLc includes two presentations for umbilical cord care: 7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine.

The 7.1% chlorhexidine digluconate solution is packaged in nozzle/dropper plastic bottle.

[3] Based on the formulation of an innovator product, Umbipro® developed by GSK available at https://www.usp-pqm.org/sites/default/files/pqms/article/gsk-chx-gel-tech-transfer-report-6-20-2019.pdf

The 7.1% chlorhexidine digluconate gel is packaged in foil laminate sachet or aluminum tube.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment, as described in Module II.

WHO-prequalified products

7.1% chlorhexidine digluconate for umbilical cord care is not included in the WHO PQP. Therefore, no WHO-prequalified products are available.

SRA-approved products

As of June 2022, there are no SRA-approved products for 7.1% chlorhexidine digluconate for umbilical cord care. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has provided a positive opinion for Umbipro® for the prevention of omphalitis (infection of the umbilical cord) in newborn infants. This application was submitted and reviewed under Article 58 of Regulation (EC) No. 726/2004, a pathway offered by EMA in cooperation with WHO for products exclusively intended for markets outside the European Union. However, this medicine product is no longer authorized[4].

The 7.1% chlorhexidine digluconate for umbilical cord care product has been developed to be used in low resource-settings where the burden of disease is high. Therefore, the product has no regulatory approval from SRAs because it is not intended for use in high-resource settings. It should be noted that there may be other chlorhexidine products approved by the SRAs, but they may be presented in different dosage forms and/or concentrations that are not indicated for umbilical cord care.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to verify SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/ formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross-check the submitted information with the corresponding NMRA websites:

[4] https://www.ema.europa.eu/en/documents/outside-eu-summary/umbipro-medicine-overview_en.pdf

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk /
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic:
- https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects manufacturers among GMP approved manufacturers via tenders (UNICEF contract awards) to supply products usually over a two- or three-year period.[5] The recent lists (from 2020) did not include 7.1% Chlorhexidine digluconate solution or gel.

It is recommended to check for updated information on the UNICEF website at the time of procurement.

Related products

Other formulations of chlorhexidine that exist in the market include:

- Topical solution (liquid, cloth, sponge applicators, swab sticks) available at concentrations 2%, 3.15%, 4%, and 5% of chlorhexidine gluconate/digluconate with and without isopropyl alcohol. Used for skin preparation for surgery, invasive procedures, and central lines to prevent hospital-acquired infections.
- Scrub solution (liquid detergent) available at concentrations 2% and 4% of chlorhexidine gluconate/digluconate with isopropyl alcohol. Used for preoperative bathing, general skin cleansing to prevent hospital-acquired infection, and preoperative hand scrub and hand disinfection to prevent the spread of microorganisms.
- Irrigation solution (chlorhexidine and cetrimide) available at concentrations 2% and 4% of chlorhexidine gluconate/digluconate. Used for irrigation of wounds to prevent infection.
- Topical cream (chlorhexidine and cetrimide) available at concentrations 0.1% of chlorhexidine gluconate/digluconate with cetostearyl alcohol. Used for wound cleaning (over-the-counter first-aid cream) to prevent infection.
- Washcloth available at concentration 2% of chlorhexidine gluconate/digluconate. Used for daily bathing in intensive care unit (ICU) patients to prevent hospital-acquired infection.
- Gauze dressing available at concentration 0.5% of chlorhexidine acetate. Used for wound or burn dressing to prevent infection.
- Catheter dressing (gel pad, foam disk, semipermeable transparent dressing) available at concentration 2% of chlorhexidine gluconate/digluconate. Used for catheter dressings to prevent hospital-acquired infection.

[5] Available at https://www.unicef.org/supply/contract-awards

- Hand rub (gel) at concentrations 0.5% and 1% of chlorhexidine gluconate/digluconate with ethanol. Used for hand sanitizing to prevent the spread of microorganisms.
- Dental solution (oral rinse or spray) at concentrations 0.12% and 0.2% of chlorhexidine gluconate/digluconate with ethanol. Used to decontaminate oral cavity to prevent ventilator-associated pneumonia and for periodontal disease and mucositis treatment.
- Concentrated stock solution available at concentration 20% of chlorhexidine gluconate/digluconate. Used for preparation of dilutions for skin cleansing and general disinfection.

It is important to note that the WHO EMLc recommends only chlorhexidine 7.1% (digluconate) delivering 4% chlorhexidine solution or gel for topical application umbilical cord care to prevent cord infection and/or sepsis and reduce neonatal mortality. Therefore, it is recommended that the procurement agency must focus on procurement of the presentations as per the WHO EMLc.

STORAGE, STABILITY, AND DEGRADATION

7.1% chlorhexidine digluconate solution and gel forms are stable at room temperature and do not require cold chain storage.

Shelf life: Generally 2 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Store below 30˚C and away from direct sunlight.

The active substance, chlorhexidine digluconate, degrades (unavoidably) via hydrolysis with multiple degradation pathways and generates a range of impurities, notably 4-chloroaniline (4-CA), which has been shown to be genotoxic and carcinogenic in non-clinical studies. The 4-CA impurity (Impurity P in the Ph.Eur. specifications for chlorhexidine digluconate solution) is known to increase with time and temperature and to be impacted by pH. The content of 4-CA in the finished product can be minimized by the following measures: controlling pH and 4-CA level in the input active substance; selection of excipients that minimize formation of 4-CA; providing instructions on appropriate storage conditions; and testing the finished product quality against specifications for a specific pH range and 4-CA content.

The active substance stability is optimal between pH 5.5 and 7.0. The pH of the active substance is important to the rate of 4-CA formation, with the primary degradation mechanisms being direct formation of 4-CA from chlorhexidine under acidic conditions and indirect 4-CA formation under alkaline conditions. To minimize levels of 4-CA and other drug-related impurities in the finished product, the pH of the input chlorhexidine digluconate active substance should be controlled as per Ph.Eur. requirements, i.e. pH 5.5–7.0.

PRODUCT SPECIFICATIONS

7.1% chlorhexidine digluconate topical solution form must meet pharmacopeial specifications,[6] such as those of the International Pharmacopeia and USP, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the two pharmacopeias are similar, except the pH limits are slightly different.

7.1% chlorhexidine digluconate topical gel form must meet pharmacopoeial specifications, such as those of the British and US Pharmacopoeias, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Table CD-51. International Pharmacopeia Specifications for Chlorhexidine Digluconate Topical Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) TLC	The principal spot obtained with solution (a) corresponds in position, appearance and intensity to that obtained with solution (b).	1.14.1 Thin-layer chromatography
b) Spectro-photometry	The absorption spectrum of the resulting solution, when observed between 200 nm and 320 nm, exhibits two maxima at about 231 nm and 255 nm, and two minima at about 218 nm and 242 nm.	1.6 Spectrophotometry in the visible and ultraviolet regions
c) HPLC	The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to chlorhexidine in the chromatogram obtained with solution (2).	1.14.4 High-performance liquid chromatography
pH	5.0–7.5	1.13 pH value
Assay	90.0–110.0%	1.14.4 High-performance liquid chromatography
Impurity P (4-chloroaniline)	In the chromatogram obtained with solution, (1) the area of any peak corresponding to 4-chloroaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.05% [m/m] of 4-chloroanilin in the amount of chlorhexidine digluconate solution used to prepare the topical solution).	1.14.4 High-performance liquid chromatography

Table CD-52. US Pharmacopeia Specifications for Chlorhexidine Digluconate Topical Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) HPLC	The retention time of the major peak for chlorhexidine from the sample solution corresponds to that of the standard solution, as obtained in the assay.	USP<621>
b) TLC	The principal spot from the Sample solution corresponds in color, size, and Rf value to that from the standard solution.	USP<201>

[6] *Chlorhexidine digluconate* is used in the International Pharmacopeia, while *chlorhexidine gluconate* is used in the British and US Pharmacopeias.

pH	5.0–7.0	USP<791>
Assay	90.0–110.0%	USP<621>
Impurities (p-chloroaniline)	The p-chloroaniline peak area from the Sample solution is NMT the p-chloroanilin peak are from the Standard solution (equivalent to NMT 500 ppm in the portion of chlorhexidine digluconate solution used to prepare the topical solution).	USP<621>

Table CD-53. US Pharmacopeia Specifications for Chlorhexidine Digluconate Topical Gel

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) UV	The UV absorption spectrum of the sample solution exhibits two maxima at 231 and 255 nm and two minima at 222 and 242 nm.	USP<197U>
b) HPLC	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay.	USP<621>
c) TLC	The principal spot of the sample solution corresponds in color, size, and Rf value to that of the standard solution.	USP<201>
pH	5.0–7.0	USP<791>
Assay	90.0–110.0%	USP<621>
Impurities (p-chloroaniline)	NMT 0.35%	USP<621>

Additional tests

Solution: Minimum fill and microbial limits should be included in the product specification.

Gel: Apparent viscosity, minimum fill, and microbial limits should be included in the product specification.

For gel packaged in sachets, the seal integrity test should be considered as in-process control.

7.1% CHLORHEXIDINE DIGLUCONATE ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

7.1% Chlorhexidine digluconate solution or gel (delivering 4% chlorhexidine) is indicated for prophylaxis of omphalitis (infection of the umbilical cord) in newborn infants.

Posology, method, and duration of administration

Posology

The recommended dose is a 3-g sachet applied once daily for 7 days. Health care providers should take account of local umbilical cord care guidelines regarding single-dose application. The first application must occur within 24 hours of birth.

For infants born at less than 32 weeks' gestation (or weighing less than 1,500 g at birth), the recommended dose is a single 3-g sachet applied once only in the first 24 hours after birth (see "Special warnings and precautions for use" section).

Method of Administration

Apply 7.1% chlorhexidine digluconate solution or gel as soon as possible within 24 hours after birth. Clean the umbilical cord stump and the skin around the base of the stump with a dry cloth prior to applying 7.1% chlorhexidine digluconate solution or gel. Apply adequate content of the sachet to ensure complete coverage of the umbilical cord, from the cut surface to the base and including the immediate surrounding abdominal skin. Wash hands before and after use.

7.1% chlorhexidine digluconate solution or gel should not be applied in combination with any other product. Occlusive dressings should not be applied to the umbilical cord stump, as doing so could increase the absorption of the product through the dermis.

Contraindications

This product should not be handled by anyone with a known history of hypersensitivity to chlorhexidine or to any of the excipients in this formulation.

Special warnings and precautions for use

For external use only. Do not inject or swallow.

Keep out of the eyes and ears and do not use over large areas of the body. If the product comes into contact with the eyes, wash out promptly and thoroughly with clean water.

There have been reports of hypersensitivity and skin irritation after topical administration of chlorhexidine, including generalized allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is not known, but available literature suggests this is likely to be very

rare. Use of the product should be discontinued and immediate medical help should be sought in case of any symptoms that may indicate an allergic reaction.

If skin irritation or redness occurs, prompt medical advice should be sought.

Treatment with chlorhexidine topical solution or gel may be associated with the development of methemoglobinemia, via degradation to 4–chloroaniline, although this has not been observed in clinical trials. This risk is likely to be increased in infants born prematurely, specifically at less than 32 weeks' gestation or weighing less than 1,500 g at birth. The treatment should be discontinued if symptoms and signs associated with methemoglobinemia, such as cyanosis or breathlessness, are observed and immediate medical advice sought.

The use of chlorhexidine solutions, both alcohol-based and aqueous, for skin antisepsis prior to invasive procedures has been associated with chemical burns in neonates. Based on available case reports and the published literature, this risk of chemical burns appears to be higher in preterm infants, especially those born before 32 weeks' gestation, and occurs within the first 2 weeks of life.

Interaction with other medicinal products and other forms of interaction

None known.

Pregnancy and lactation

Not intended for this patient population.

Effects on ability to drive and use machines

Not relevant.

Undesirable effects

Adverse reactions

Adverse reactions are classified by system organ class. Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented below.

Frequencies were defined as follows: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

The adverse reactions shown below have been associated with post-marketing data from different marketed chlorhexidine formulations (antiseptic solution, antiseptic cream, and antiseptic mouthwash). No post-marketing data are available for the 7.1% gel formulation.

Immune system disorders

- Hypersensitivity and anaphylaxis: frequency not known.

Skin and subcutaneous tissue disorders:

- Allergic skin reactions such as erythema and skin irritation: frequency not known.

Description of selected adverse reactions

The most serious reported adverse reactions to medicinal products or devices containing chlorhexidine are systemic hypersensitivity/anaphylaxis; see "Special warnings and precautions for use" section. Signs of a hypersensitivity reaction include rash, urticaria, angioedema, difficulty breathing, collapse, or loss of consciousness.

Overdose

This has not been reported.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of chlorhexidine products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on chlorhexidine digluconate solution or gel for umbilical cord care.

API

The API for 7.1% chlorhexidine digluconate solution or gel for umbilical cord care is 20% chlorhexidine digluconate solution.

Chlorhexidine digluconate solution (API) is not included in the WHO PQP. Therefore, no WHO-prequalified chlorhexidine digluconate solution exists.

Four manufacturers of chlorhexidine digluconate solution have obtained a certificate of suitability to monographs of the European Pharmacopeia (CEP), confirming suitable quality for use in medicinal product.

Table CD-54. Manufacturers of Chlorhexidene Digluconate Solution API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Chlorhexidine digluconate solution (monograph number 658)	Medichem, S.A. Sant Joan Despí, Spain	R1-CEP 1993-009-Rev 04	2/16/2009	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	R.N. Laboratories Mumbai, India	R1-CEP 2006-171-Rev 02	05/17/2018	Chemistry
Chlorhexidine digluconate solution CDG (monograph number 658)	Medichem, S.A. Sant Joan Despí, Spain	R0-CEP 2017-128-Rev 01	12/20/2018	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Bajaj Healthcare Limited Thane (West), India	R0-CEP 2017-074-Rev 00	6/28/2019	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Evonik Operations GMBH Essen, Germany	R1-CEP 2001-343-Rev 05	8/31/2020	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Xttrium Laboratories, INC. Mount Prospect, USA	R0-CEP 2020-179-Rev 00	11/10/2021	Chemistry

Other manufacturers of chlorhexidine digluconate solution should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

Chlorhexidine digluconate solution must meet pharmacopeia specifications,[2] such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Note: 4-chloroaniline (4CA) has been shown to be genotoxic and carcinogenic in nonclinical studies. Therefore, it is suggested to procure API with the lowest 4CA levels.[3]

Excipients

The typical excipients of 7.1% chlorhexidine digluconate solution or gel for umbilical cord care are as follows. There are no special concerns regarding the excipients.

Table CD-55. Excipients of 7.1% Chlorhexidine Digluconate Solution or Gel

INGREDIENT	FUNCTION
Purified water	Vehicle
Sodium acetate trihydrate	pH enhancer
Sodium hydroxide	pH adjustment
Guar gum	Thickening agent—viscosity enhancer (used for the gel formulation)
Benzalkonium chloride	Preservative (optional)

Note: sodium hydroxide could lead to the formation of turbid solution and decrease the chemical stability of the drug product in reference to 4CA and total impurities content. 0.1% w/w sodium acetate trihydrate is a suitable alternative to adjust the pH, providing better stability with respect to 4CA content.[9]

The quality of excipients should be compliant with recognized pharmacopeias (Ph.Int., Ph.Eur./BP, or USP).

Sodium acetate trihydrate is used as the pH stabilizer in the innovator product, as it was shown to result in the lowest level of drug-related impurities.[4] The use of buffer salts for maintaining the pH of the solution should be restricted due to the incompatibility of chlorhexidine gluconate with other anionic materials such as borates, phosphates, acetates, nitrates, and chlorides.

For the gel formulation, guar gum is an economical thickener and stabilizer for producing the gel form. The very high viscosity attained at low concentrations makes guar gum an excellent thickener. The other advantage of guar gum is that it is non-ionic, so it is stable over a wide pH range.

The source of guar gum may impact active substance stability. The guar gum may contain acidic impurities as a carryover from the extraction/purification process, potentially causing the

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.
[2] Chlorhexidine digluconate is used in the International and European Pharmacopeias, while chlorhexidine gluconate is used in the US Pharmacopeia
[3] PQM. GSK Chlorhexidine Digluconate (7.1%) Gel Technology Transfer Report. 2018. U.S. Pharmacopeial Convention. The Promoting the Quality of Medicines Program. Rockville, Maryland.
[4] EMA assessment report of Umbipro®.

degradation of chlorhexidine. Studies using guar gum from different suppliers are recommended as part of the finished product development.

Some formulations may contain benzalkonium chloride as a preservative. However, a study by PATH[5] indicated that benzalkonium chloride did not offer added value as a preservative, since it was not imparting additional stability to the chlorhexidine formulation. Since the concentration of chlorhexidine in the formulation is very high (4%), chlorhexidine will probably kill any bacteria with or without benzalkonium chloride, thereby making the role of benzalkonium chloride indistinguishable.

It should be noted that when benzalkonium chloride is used in the formulation, a light brown coloration of the solution can be observed, due to the interaction of chlorhexidine with chloride from benzalkonium chloride. The discoloration does not adversely affect the potency of chlorhexidine. Product specifications may need to be changed to accommodate the appearance characteristics of the chlorhexidine digluconate solution or gel if used in combination with benzalkonium chloride.

Manufacturing process

Both chlorhexidine digluconate solution and gel are straightforward products to manufacture, involving a standard manufacturing process.

Solution and gel form have very similar manufacturing processes, with the only difference being in the step where guar gum is added to thicken the product into a gel.

For solution form, the typical manufacturing process involves preparing chlorhexidine digluconate solution in water, followed by pH adjustment and filling into bottles.

For gel form, the typical manufacturing process involves dissolving sodium acetate trihydrate in water, followed by dispersion and hydration of guar gum. The solution is heated at this stage to aid hydration of the guar gum. The resultant gel is then cooled, before addition and mixing of chlorhexidine digluconate solution. The gel is subsequently de-aerated using vacuum and then discharged into a holding vessel prior to being filled into aluminum tube or foil laminate sachets using suitable form-fill-seal packaging equipment.

Large-scale production of the gel formulation containing guar gum requires specialized equipment (high-pressure homogenizer). High-pressure homogenization is essential to the quality and stability of the gel formulation since this is a very effective way to create homogeneity in the gel texture while at the same time producing a very stable product, compared to the traditional devices such as agitators, stirrers, rotor-stator devices, or colloid mills. The result is a homogeneous, effective product with superior stability and shelf life.

Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture. When adding/dispersing the guar gum, the gel temperature and high-shear mixing time should be well defined. The gel should be cooled before the addition of chlorhexidine digluconate solution.

Packaging

The primary package material must comply with USP, Ph.Eur., and/or European Community requirements. Since sunlight adversely affects the stability of chlorhexidine digluconate, transparent primary containers should be avoided.

[5] PATH. 2010. “Stability Data of Chlorhexidine Formulations: PATH Summary.” PATH: Seattle.

Notes:

- *The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[6, 7]

Solution

The 7.1% chlorhexidine digluconate solution is packaged in an HDPE bottle with polypropylene screw closure.

The nozzle/dropper bottles provide the best product coverage on the umbilical stump. The nozzle minimizes occasions in which users directly contact the umbilical cord. However, depending upon the country, users may associate the small (single-day) application size nozzle/dropper bottles with newborn eye or ear drops. Therefore, clear instructions should be put on the product label.

Spray bottles work only in the upright position and might make it difficult for users to achieve complete coverage of the cord stump. Wide-mouth bottles may increase the risk of product contamination and spillage.

Gel

The 7.1% chlorhexidine digluconate gel is packaged in a foil laminate sachet or aluminum tube.

Aluminum tubes are commonly used for semi-solid pharmaceuticals. However, depending upon the country, users may associate the small (single-day) application size tubes with newborn eye ointment. Therefore, clear instructions should be put on the product label.

Sachets could be a lower-cost option. However, depending on the country, sachets might not be commonly used for pharmaceuticals; therefore, manufacturers might not have the appropriate equipment, and users might associate sachets with cosmetics rather than medicines, leading to confusion.

Note: The risk assessment for potential presence of leachables from the container closure system and from the manufacturing process should be carried out.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API in the same molar concentration and the same excipients in similar concentrations as in the comparator product.

Umbipro®, the original product developed GlaxoSmithKline is not available in SRA countries. However, in collaboration with the U.S. Pharmacopeial Convention (USP) Promoting the Quality of

[6] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[7] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

Medicines (PQM) Program, GlaxoSmithKline has provided a Technology Transfer Report[8] that is available in the public domain. This document addresses the development of the formulation, analytical testing, key information for the manufacturing and primary packaging processes, and describes Clinical and Nonclinical Studies references. In addition, the PQM has also issued a report describing technical information to support the dossier preparation[9]. In the absence of a comparator product available in SRA countries, both guidelines are suitable references to support the chlorhexidine digluconate 7.1% gel product development and submission.

[8] PQM. GSK Chlorhexidine Digluconate (7.1%) Gel Technology Transfer Report. 2018. U.S. Pharmacopeial Convention. The Promoting the Quality of Medicines Program. Rockville, Maryland.

[9] PQM+. 2020. Chlorhexidine digluconate (7.1%) Gel Dossier Aid. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention

AMOXICILLIN

DISPERSIBLE TABLETS 250 MG

GENERAL PRODUCT INFORMATION

Amoxicillin is a penicillin-class, effective broad-spectrum antibiotic, which is commonly prescribed to children for treatment of pneumonia and other illnesses, including other bacterial infections of the ears, sinuses, throat, urinary tract, skin, abdomen, and blood. In 2014, WHO published its recommendations for home treatment of pneumonia, establishing amoxicillin as the recommended treatment for pneumonia in children under five.[1] WHO recommends amoxicillin 250 mg dispersible tablets as the most convenient formulation to treat childhood pneumonia in community settings, and especially in remote areas where no reliable sources of clean water and electricity are available. Tablets are cheaper and easier to store and to transport compared with bottled amoxicillin oral suspension. Moreover, minimal manipulation is required prior to the use of a dispersible tablet: it is readily and easily swallowed after adding a small amount of water. This alleviates the need to break or crush adult tablets into smaller pieces before administering a dose to a child or use measuring devices supplied with liquid formulations, which are not accurate and can cause dosing errors.

Amoxicillin 250 mg dispersible tablet is included in the WHO Essential Medicines List and Priority Medicines List for Children.[2] It is also considered an essential medicine for child health by the UN Commission on Life-Saving Commodities for Women and Children.

[1] WHO. *Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities*. Geneva: WHO, 2014. Available at http://www.who.int/maternal_child_adolescent/documents/child-pneumonia-treatment/en/.
[2] WHO. *Priority Medicines for Mothers and Children 2011.* Geneva: WHO, 2011. Available at http://www.who.int/maternal_child_adolescent/documents/emp_mar2011.1/en/.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by UNICEF and those with a proven record of quality products.

2. Procurers should ensure the candidate amoxicillin dispersible tablets have been evaluated by the manufacturer for taste masking. The taste of a dispersible tablet is a crucial parameter that will condition the acceptability by the child and the adherence to treatment. Taste masking is therefore necessary by adding fruit flavors and/or sweeteners to the formulation. The flavors or sweeteners must be common to the areas where the product will be used. Acceptance of the product first by mothers is critical to adherence to treatment by children. A short guide on how to evaluate the taste is described in the Annex.

3. Procurers need to focus on product quality to ensure that it is safe for patient use.

KEY QUALITY CONSIDERATIONS

Product specification

The product must comply with the quality specifications as detailed in the "Product Specifications" section below.

Procurers should ensure products are tested for disintegration time according to the compendial monograph, and the certificate of analysis is checked for disintegration data. Amoxicillin dispersible tablets should completely disintegrate within three minutes when put in a small amount (5–10 mL) of liquid (clean water or milk).

Preference should be given to colorant-free formulations.

Packaging and labeling

Procure tablets only in dispersible form. Amoxicillin dispersible tablets are the most suitable form for treatment of infants and young children. Compared with amoxicillin oral suspension forms, dispersible tablets have advantages in product stability and storage.

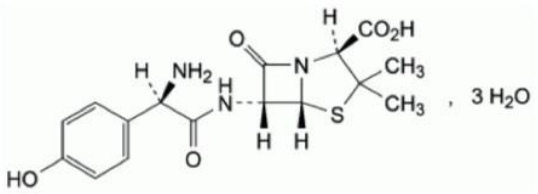
Amoxicillin dispersible tablets that are procured should be packaged in blisters only, as dispersible tablets are water sensitive. Amoxicillin dispersible tablets packaged in bottles or other similar multidose containers will be subjected to humidity each time the container is opened and may start to disintegrate.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify with manufacturers that there is satisfactory stability data to support shelf life and storage conditions. The standard shelf life of amoxicillin dispersible tablets is three years when stored at room temperature.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Name of the Medicinal Product	Amoxicillin 250-mg dispersible tablets
Chemical Name	Amoxicillin trihydrate (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]-amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate
Chemical Structure	$C_{16}H_{19}N_3O_5S$, $3H_20$ 
Pharmaceutical Form	Dispersible tablets
Qualitative and Quantitative Composition	Each tablet contains amoxicillin trihydrate equivalent to 250 mg amoxicillin. List of typical excipients[3]: – Aspartame – Colloidal anhydrous silica – Magnesium stearate – Microcrystalline cellulose – Crospovidone – Other sweeteners – Flavors
Packaging and Presentation	Amoxicillin dispersible tablets are usually packed in blisters (aluminum/PVC) or strips (aluminum) of 10 tablets.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

Amoxicillin dispersible tablet 125 mg (scored) and 250 mg (scored) are included in the WHO invitation to manufacturers of medicinal products for treatment of infections in newborn and young infants and childhood pneumonia, to submit an Expression of Interest (EOI) for product evaluation for WHO PQ. As of June 2022, no WHO-prequalified amoxicillin products are available.

[3] Based on the formulation of amoxicillin dispersible tablets approved by EMA and MHRA, although for different strengths.

SRA-approved products

As of June 2022, no SRA-approved amoxicillin 250-mg dispersible tablets are available [4].

When a manufacturer claims that a product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA

Procurers may cross-check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- UK MHRA: https://products.mhra.gov.uk/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects manufacturers among GMP approved manufacturers via tenders (UNICEF contract awards) to supply products usually over a two- or three-year period.[5] The recent lists (from 2020) did not include Amoxicillin 250 mg dispersible tablets.

It is recommended to check for updated information on the UNICEF and WHO PQP websites at the time of procurement.

Related products

Amoxicillin is formulated into conventional capsules ("amoxicillin caps"), tablets ("amoxicillin tabs"), powder for oral suspension ("amoxicillin OS"), and dispersible tablets ("amoxicillin DT"). Many other forms are currently available in the market, including powder for solution for injection or infusion, syrups, sachets, and oral drops.

Amoxicillin caps	– Amoxicillin capsules are the most widely available pharmaceutical form, available in strengths of 125 mg–1,000 mg. – It is the preferred formulation for adults and can be taken without water if necessary.

[4] Other strengths of amoxicillin dispersible tablets (e.g., 750 mg, 1,000 mg) were found approved and marketed in SRA countries and are indicated for treatment of various bacterial infections.
[5] https://www.unicef.org/supply/contract-awards

Amoxicillin tabs	– Amoxicillin tablets are another conventional form, often available with scoring, available in strengths of 500 mg–1,000 mg. – Scored tablets allow pharmaceutical tablets to be broken and dosing adjusted according to prescription. – They are not as extensively used as capsules and often need to be taken with water.
Amoxicillin OS	– Amoxicillin powder for oral suspension is at present the most commonly used pediatric formulation. – It is administered as a liquid, which facilitates the treatment of children and those with difficulties swallowing solid dosage forms like tablets or capsules. – It is available in the strengths of 125 mg/5 mL to 500 mg/5 mL.

In the WHO Model List of Essential Medicines for Children, the following dosage forms for amoxicillin are listed[6]:

- Powder for oral liquid: 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL
- Solid oral dosage form: 250 mg; 500 mg (as trihydrate)
- Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial

Because the dosage of amoxicillin is based on the child's weight, and because of the potential risks of microbial resistance with underdosing and of toxicity with overdosing, it is crucial that the pediatric formulations have flexibility for dose adjustment. The use of the conventional tablet dosage form often involves breaking a hard adult tablet into smaller pieces, then crushing and adding it to food or liquid; this can lead to inaccuracies in dosing. Liquid dosage forms make weight-based dosing much easier; however, measuring devices supplied with liquid medicines are not accurate and significant under- or overdosing can occur. WHO therefore recommends dispersible tablet dosage forms as the most convenient formulation for children, as they provide greater dosage accuracy, they are less costly than tablets, they have better stability and shelf life than liquids, and they are less bulky to ship and store.

Advantages of amoxicillin dispersible tablets compared to oral suspensions can be described as follows:

- Amoxicillin dispersible tablets are cheaper than its equivalent oral suspensions.
- They offer logistical and supply chain advantages in terms of volume and weight.
- They are also designed to accommodate patients with difficulties in swallowing.
- Amoxicillin dispersible tablets facilitate and simplify community case management (CCM) and provide greater dosage accuracy compared to oral suspensions, which have to be manually measured and mixed.
- Amoxicillin dispersible tablets do not need refrigeration.

STORAGE, STABILITY, AND DEGRADATION

Amoxicillin dispersible tablets have no cold chain storage complications.

Shelf life: 36 months, depending on the manufacturer. It is recommended to check the product label before use.

[6] For use as treatment of community acquired pneumonia (mild to moderate), community-acquired pneumonia (severe), complicated severe acute malnutrition, otitis media, pharyngitis, sepsis in neonates and children, sinusitis, progressive apical dental abscess, and uncomplicated severe acute malnutrition.

Storage condition: Do not store above 30˚C.

Significant breakage of the beta-lactam ring of amoxicillin can occur in hot and humid climatic conditions if inadequate types of packaging are used and storage occurs under inappropriate conditions.

PRODUCT SPECIFICATIONS

The product must meet the USP specifications[7], or the equivalent thereof.

Furthermore, evaluation of taste masking and taste acceptability of the formulation should be conducted during product development to ensure acceptance of the product by children. A short guide on how to evaluate the taste of a medicine has been published by the EMA Committee for Medicinal Products for Human Use, which is summarized in the Annex.

Table A-56. US Pharmacopeia Specifications for Amoxicillin Dispersible Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (TLC)	The Rf value of the principal spot of the sample solution corresponds to that of the standard solution.	USP<201>
Assay	90.0–110.0%	HPLC, USP<621>
Disintegration	Not more than 3 minutes	USP<701>
Dissolution	Not less than 80% (Q) of the labeled amount of amoxicillin is dissolved.	USP<711>
Uniformity of dosage units	Meet the requirements	USP<905>
Dispersion fineness	A smooth dispersion that passes through a no. 25 sieve is obtained.	As per USP monograph of amoxicillin tablets for oral suspension

[7] As of June 2022, there are no monographs of amoxicillin dispersible tablets published in the International and British Pharmacopeias. Please check updated information at http://apps.who.int/phint/en/p/about/ and in the British Pharmacopeia.

AMOXICILLIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

WHO recommends oral amoxicillin as the treatment for childhood fast-breathing and chest-indrawing pneumonia.

Oral amoxicillin is also indicated for the treatment of the following infections in adults and children:

- Acute sinusitis
- Acute malnutrition in infants, children or adolescents (complicated)
- Acute malnutrition in infants, children or adolescents (uncomplicated)
- Bacterial pneumonia (community-acquired pneumonia – mild to moderate)
- Periapical abscess without sinus
- Acute otitis media
- Acute pharyngitis
- Chronic obstructive pulmonary disease with acute exacerbation
- Dental infections
- Sepsis without septic shock (co-prescribed with Gentamicin)
- Bacterial pneumonia (community-acquired pneumonia – severe) in children (co-prescribed with Gentamicin)

Oral amoxicillin is also indicated for the prophylaxis of endocarditis.

Posology, method, and duration of administration

Table A-57. Doses of Amoxicillin for Children 2-59 Months of Age with Pneumonia

CATEGORY OF PNEUMONIA	AGE/WEIGHT OF CHILD	DOSAGE OF AMOXICILLIN DISPERISBLE TABLETS (250 MG)
Fast-breathing pneumonia	2–12 months (4 to < 10 kg)	1 tab twice a day x 5 days (10 tabs)
	12 months–5 years (10–19 kg)	2 tabs twice a day x 5 days (20 tabs)
Fast-breathing and chest-indrawing pneumonia	2–12 months (4 to< 10 kg)	1 tab twice a day x 5 days (10 tabs)
	12 months–3 years (10 to < 14 kg)	2 tabs twice a day x 5 days (20 tabs)
	3–5 years (14–19 kg)	3 tabs twice a day x 5 days 30 tabs)

For other indications

The dose of amoxicillin selected to treat an individual infection should take into account:

- Expected pathogens and their likely susceptibility to antibacterial agents
- Severity and site of infection
- Age, weight, and renal function of the patient; as shown below

The duration of therapy should be determined by the type of infection and response of the patient, and should generally be as short as possible. Some infections require longer periods of treatment.

Children < 40 kg

Children may be treated with capsules, dispersible tablet suspensions, or sachets. Pediatric suspension is recommended for children under 6 months of age. Children weighing 40 kg or more should be prescribed the adult dosage.

Table A-58. Recommended Doses for Children < 40 Kg

INDICATION*	DOSE
Acute bacterial sinusitis, acute otitis media, community-acquired pneumonia, acute cystitis, acute pyelonephritis, and dental abscess with spreading cellulitis	20–90 mg/kg/day in divided doses**
Acute streptococcal tonsillitis and pharyngitis	40–90 mg/kg/day in divided doses**
Typhoid and paratyphoid fever	100 mg/kg/day in three divided doses
Prophylaxis of endocarditis	50 mg/kg orally, single dose 30–60 minutes before procedure
Lyme disease	Early stage: 25–50 mg/kg/day in three divided doses for 10–21 days Late-stage (systemic involvement): 100 mg/kg/day in three divided doses for 10–30 days

** Consideration should be given to the official treatment guidelines for each indication.*
*** Twice-daily dosing regimens should only be considered when the dose is the upper range.*

Adults and children ≥ 40 kg

Table A-59. Recommended Doses for Adults and Children ≥ 40 Kg

INDICATION*	DOSE
Acute bacterial sinusitis, acute pyelonephritis, dental abscess with spreading cellulitis	250–500 mg every 8 hours, 750 mg–1 g every 12 hours For severe infections 750 mg–1 g every 8 hours
Acute otitis media, acute streptococcal tonsillitis and pharyngitis, and acute exacerbations of chronic bronchitis	500 mg every 8 hours, 750 mg–1 g every 12 hours For severe infections 750 mg–1 g every 8 hours for 10 days
Community-acquired pneumonia	500 mg–1 g every 8 hours
Typhoid and paratyphoid fever	500 mg–2 g every 8 hours
Prosthetic joint infections	500 mg–1 g every 8 hours
Prophylaxis of endocarditis	2 g orally, single dose 30–60 minutes before procedure
Lyme disease	Early stage: 500 mg–1 g every 8 hours up to a maximum of 4 g/day in divided doses for 14 days (10–21 days)

INDICATION*	DOSE
	Late-stage (systemic involvement): 500 mg–2 g every 8 hours up to a maximum of 6 g/day in divided doses for 10–30 days

**Consideration should be given to the official treatment guidelines for each indication*

Renal impairment

Table A-60. Recommended Doses for Renal Impairment

GFR (ML/MIN)	CHILDREN < 40 KG*	ADULTS AND CHILDREN ≥ 40 KG
Greater than 30	No adjustment necessary	No adjustment necessary
10–30	15 mg/kg given twice daily (maximum 500 mg twice daily)	Maximum 500 mg twice daily
> 10	15 mg/kg given as a single daily dose (maximum 500 mg)	Maximum 500 mg/day

** In the majority of cases, parenteral therapy is preferred*

Hemodialysis

In patients receiving hemodialysis, amoxicillin may be removed from the circulation by hemodialysis.

Table A-61. Recommended Dose for Adults and Children ≥ 40 Kg

15 MG/KG/DAY GIVEN AS A SINGLE DAILY DOSE.
Prior to hemodialysis, one additional dose of 15 mg/kg should be administered. To restore the circulating drug levels, another dose of 15 mg/kg should be administered after hemodialysis.

In patients receiving peritoneal dialysis: amoxicillin maximum 500 mg/day.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Contraindications

Hypersensitivity to the active substance, to any of the penicillins, or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g., cephalosporin, carbapenem, or monobactam).

Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible, or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose, and throat.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses, or in patients with predisposing factors (e.g., history of seizures, treated epilepsy or meningeal disorders).

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment.

Skin reactions

The occurrence at treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires amoxicillin discontinuation and contraindicates any subsequent administration.

Amoxicillin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. It results directly from the bactericidal activity of amoxicillin on the causative bacterium of Lyme disease, the spirochete *Borrelia burgdorferi*. Patients should be reassured this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during, or subsequent to, the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician consulted, and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Crystalluria

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false-positive readings are common with chemical methods.

When testing for the presence of glucose in urine during amoxicillin treatment, it is recommended that enzymatic glucose oxidase methods be used.

The presence of amoxicillin may distort assay results for estriol in pregnant women.

Important information about excipients

This medicinal product contains aspartame, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria.

Interaction with other medicinal products and other forms of interaction

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

Penicillins may reduce the excretion of methotrexate, causing a potential increase in toxicity.

Pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitization. Consequently, diarrhea and fungus infection of the mucous membranes are possible in the breastfed infant, so that breastfeeding might have to be discontinued. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

Undesirable effects

The following categories are used for stating the frequency of undesirable effects: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations

Very rare: mucocutaneous candidiasis.

Blood and lymphatic system disorders

Very rare: reversible leucopenia (including severe neutropenia or agranulocytosis), reversible trombocytopenia, and hemolytic anemia. Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare: severe allergic reactions, including angioneurotic edema, anaphylaxis, serum sickness, and hypersensitivity vasculitis.

Not known: Jarisch-Herxheimer reaction.

Nervous system disorders

Very rare: hyperkinesia, dizziness, and convulsions.

Gastrointestinal disorders

Clinical trial data

- * Common: diarrhea and nausea

- * Uncommon: vomiting

Post-marketing data

- Very rare: antibiotic-associated colitis (including pseudomembraneous colitis and hemorrhagic colitis). For oral formulations only, black hairy tongue. For dispersible tablets and oral suspension only, superficial tooth discoloration**.

Hepatobiliary disorders

Very rare: hepatitis and cholestatic jaundice; a moderate rise in AST and/or ALT.

Skin and subcutaneous tissue disorders

Clinical trial data

- * Common: skin rash
- * Uncommon: urticaria and pruritus

Post-marketing data

- * Very rare: skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, and acute generalized exanthematous pustulosis (AGEP)

Renal and urinary tract disorders

Very rare: interstitial nephritis and crystalluria.

Notes

** The incidence of these adverse events was derived from clinical studies involving a total of approximately 6,000 adult and pediatric patients taking amoxicillin.*

*** For dispersible tablets and oral suspension formulations only, superficial tooth discoloration has been reported in children. Good oral hygiene may help prevent tooth discoloration as it can usually be removed by brushing.*

Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting, and diarrhea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin can be removed from the circulation by hemodialysis.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of amoxicillin products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on amoxicillin dispersible tablets.

API

Amoxicillin is included in the WHO PQP. As of June 2022, there is no WHO-prequalified amoxicillin API.

Several manufacturers of amoxicillin API have obtained a certificate of suitability for monographs of the European Pharmacopeia (CEP), confirming their quality is suitable for use in medicinal products.

Table A-62. Manufacturers of Amoxicillin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Amoxicillin trihydrate, powder material, compacted grade A, compacted for direct compression (monograph number 260)	Fersinsa GB S.A. De C.V. MX 25900 Ramos Arizpe, Mexico	R2-CEP 1995-030-Rev 02	6/2/2014	Chemical
Amoxicillin trihydrate, material codes 472191, 472188, 472205, 451787, 440017, 440029, 452360 (monograph number 260)	Sandoz Industrial Products S.A. ES 08520 Les Franqueses Del Vallès, Spain	R2-CEP 1995-034-Rev 06	11/12/2015	Chemical
Amoxicillin trihydrate (monograph number 260)	Aurobindo Pharma Ltd IN 500 038 Hyderabad, India	R1-CEP 2007-147-Rev 03	10/3/2017	Chemical
Amoxicillin trihydrate (monograph number 260)	GlaxoSmithKline Research & Development Ltd, GB TW8 9GS London, UK	R1-CEP 2000-010-Rev 04	6/4/2018	Chemical
Amoxicillin trihydrate, compacted (monograph number 260)	Zhuhai United Laboratories Co, Ltd CN 519 040 Sanzao Town, China	R1-CEP 2007-191-Rev 03	2/6/2019	Chemical
Amoxicillin trihydrate (monograph number 260)	Centrient Pharmaceuticals Netherlands B.V. Delft NL	R1-CEP 2001-367-Rev 05	3/21/2019	Chemical
Amoxicillin trihydrate Enzymatic process (monograph number 260)	Aurobindo Pharma Ltd IN 500 038 Hyderabad, India	R0-CEP 2017-037-Rev 01	16/4/2019	Chemical
Amoxicillin trihydrate (monograph number 260)	Centrient Pharmaceuticals Netherlands B.V. Delft NL	R1-CEP 2007-226-Rev 03	4/24/2019	Chemical
Amoxicillin trihydrate (monograph number 260)	Inner Mongolia Changsheng Pharmaceutical Co., Ltd. Tuoketuo, China	R1-CEP 2007-315 - Rev 02	1/31/2020	Chemical

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Amoxicillin trihydrate (monograph number 260)	Fersinsa GB S.A. De C.V. Ramos Arizpe MX	R0-CEP 2018-178-Rev 01	8/19/2020	Chemical
Amoxicillin trihydrate, micronized, normal and high-density powder (monograph number 260)	Zhuhai United Laboratories Co, Ltd. CN 519 040 Sanzao Town, China	R1-CEP 2006-039-Rev 02	10/16/2020	Chemical
Amoxicillin trihydrate Enzymatic process (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R1-CEP 2014-220-Rev 00	9/11/2020	Chemical
Amoxicillin trihydrate Enzymatic process (monograph number 260)	GlaxoSmithKline Research and Development Ltd GB UB11 1BT Stockley Park, UK	R1-CEP 2015-064-Rev 00	3/3/2021	Chemistry
Amoxicillin trihydrate (monograph number 260)	Sinopharm Weiqida Pharmaceutical CO., LTD. Datong, China	R0-CEP 2019-244-Rev 01	9/29/2021	Chemistry
Amoxicillin trihydrate Enzymatic process, compacted (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R1-CEP 2017-009-Rev 00	3/2/2022	Chemistry
Amoxicillin trihydrate (monograph number 260)	Teva Pharmaceutical Industries Ltd Tel Aviv - Jaffa, Israel	R1-CEP 2004-146-Rev 02	3/7/2022	Chemistry
Amoxicillin trihydrate compacted (monograph number 260)	Inner Mongolia Changsheng Pharmaceutical CO., LTD. Tuoketuo, China	R1-CEP 2016-310-Rev 00	3/8/2022	Chemistry
Amoxicillin trihydrate Powder, compacted (monograph number 260)	The United Laboratories (Inner Mongolia) CO., LTD. Bayannaoer, China	R1-CEP 2012-078-Rev 02	4/13/2022	Chemistry
Amoxicillin trihydrate compacted (monograph number 260)	Sinopharm Weiqida Pharmaceutical CO., LTD. Datong, China	R0-CEP 2021-461 - Rev 00	5/18/2022	Chemical

Other manufacturers of amoxicillin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

Amoxicillin API must meet pharmacopeia specifications such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Preferably, the amoxicillin trihydrate is used as a pelletized form. The equilibrium relative humidity (ERH) of the amoxicillin trihydrate used as API should be carefully controlled by appropriate drying so that it does not adversely affect other aspects of the formulation. Preferably, the ERH is less than 30%, ideally from 10% to 20%.

Due to the sensitivity of this API to temperature and humidity, the U.S. Pharmacopeial Convention (USP) recommends using compacted or directly compressible API for manufacturing of dispersible tablets.[2]

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.
[2] Promoting the Quality of Medicines (PQM). Product Information Report: Amoxicillin. 2017. U.S. Pharmacopeial Convention. Rockville, Maryland.

Excipients

The excipients of amoxicillin dispersible tablets include typical tablet diluent (microcrystalline cellulose), disintegrant (e.g., colloidal anhydrous silica, crospovidone), and lubricant (e.g., magnesium stearate).

Amoxicillin dispersible tablets may contain one or more suitable flavors and sweeteners for greater acceptability. The label should indicate the name(s) and amount(s) of any added substances(s). Such added substances:

- Should be harmless in the amounts used
- Should not exceed the minimum quantity required for providing their intended effect
- Should not impair the bioavailability or the therapeutic efficacy or safety of the preparation
- Should not interfere with the assays and tests used to determine compliance with the pharmacopeial standards

The quality of the raw materials in the formulation can affect the product stability. The insoluble excipients can decrease the dissolution rate of amoxicillin trihydrate. Therefore, the formulation should contain as few excipients as possible, to minimize adverse effects on the product stability.

Manufacturing process

The amoxicillin dispersible tablets should be manufactured using dry granulation or a direct compression method. The U.S. Pharmacopeial Convention (USP) report on Amoxicillin[9] also mentions manufacturing of amoxicillin dispersible tablets using dry granulation followed by tablet compression as a viable route. A wet granulation method is not recommended because the formulation is highly sensitive to moisture and temperature conditions.

Careful monitoring and control of humidity during manufacturing and packaging is required.

Note: The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Amoxicillin dispersible tablets are usually packed in blisters (aluminum/PVC) or strips (aluminum). Considering that the product needs to be protected from exposure to humidity, the Alu-Alu blister is considered a suitable packaging configuration as it is considered impermeable and highly protective[9].

Suitability of the container should be demonstrated, including the following properties:

Safety

- Declarations of compliance with appropriate food additive regulations (e.g., US FDA or EU regulations).

Protection

- Water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671>

Compatibility

- Accelerated and long-term stability data for the packaged finished products.

Bioequivalence requirements

Amoxicillin is a BCS Class I drug (high solubility, high permeability), which is eligible for a biowaiver provided:

1. The dosage form is rapidly dissolving (as defined below) and the dissolution profile of the multisource (generic) product is similar to that of the comparator product in aqueous buffers at pH 1.2, pH 4.5, and pH 6.8 using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);
2. If both the comparator and the multisource products are very rapidly dissolving (as defined below) the two products are deemed equivalent and a profile comparison is not necessary.

Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 15 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 30 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Pharmacopeial buffers (e.g., Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (i.e., capsules or caplets) due to the possibility of cross-linking.

It should be demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API, and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting

absorption (e.g., by effects on gastrointestinal motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

It is therefore recommended that the excipients employed be present in either the comparator product or in other products that contain the same API as the multisource product and that have marketing authorizations in ICH-associated countries. Excipients that might affect the bioavailability of the API (e.g., mannitol, sorbitol, or surfactants) should be identified and an assessment of their impact should be provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

WHO has established the following options as acceptable comparator products:

- Amoxil/Clamoxyl (amoxicillin 125mg/5ml, 250mg/5 ml, and 500mg/5ml powder for oral suspension (bottle), 250 and 500 mg powder for oral suspension in sachet, GlaxoSmithKline Pharmaceuticals)
- Amoxicillin pediatric 50mg/ml powder for oral suspension (Teva Pharmaceuticals Inc., US). The recommended comparator product is approved by US FDA; the comparator product should be obtained from the US.

Notes:

- *The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[3, 4]

EMA guidance on the evaluation of taste masking[5]

Qualitative evaluation of the taste by a taste panel

Consumer testing is acknowledged as providing the best population to assess a product. Consumers are regarded as individuals who are prescreened to be actual users of the product tested, with particular interest as to product quality. In line with this definition and taking into consideration the sensory differences between adults and children, it is evident that the children as a target population are regarded as the most suitable panel for taste assessment of pediatric formulations.

Recommendations for performing taste trials in children

To design a palatability study in children the following parameters need to be considered as key elements:

- The test should be short in order to match children's attention span.

[3] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[4] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update
[5] European Medicines Agency. 2005. *Reflection Paper: Formulation of Choice for the Paediatric Formulation.* EMA/CHMP/PEG/194810/2005. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf.

- As children are easily distracted, the test has to be intrinsically motivating and "fun" to do.
- The procedure has to be as easy as possible so that even very young children (e.g., preschoolers) can understand it.
- To ensure reliable assessment preventing confusion by the children and taste fatigue, the number of variants to be tested should be limited to a maximum of four.

Palatability studies are not described in any regulatory guidance but must be considered as clinical studies performed by qualified personnel with ethical committee approval, informed consent from parents or guardians and assent from the child as appropriate. There may be ethical difficulties in designing suitable safe studies in which children can easily participate.

Participation and test performance

Generally, children aged 4 years and older are considered to be able to participate in taste trials. Younger children are very often shy and reluctant. Furthermore, their ability to understand and follow the guidance is sometimes limited; they also may lose interest or have difficulty concentrating during an entire testing period. The failure rate varies up to 50% depending on the design and duration of the test. In addition, they are often unable to communicate their feelings and preferences.

To increase children's understanding and motivation, it is recommended to start with either high concentrations of the testing agent to be assessed (flavor or sweetener) or with known compounds (e.g., commonly used flavors) followed by the more specific, unusual one (e.g., strawberry or cherry followed by passion fruit). In some cases, to begin the test with high concentrations of the testing agent (e.g., sweetener) would be inappropriate due to the unpleasant sweet taste or the bitter aftertaste. Procedures to remove the previous taste may include repeated rinsing of the mouth, eating of salty crackers, and a sufficiently long interval between sessions.

Sensory evaluation: affective and analytical testing, and ranking

Probably the most critical item in sensory evaluation is defining the objective. The test objective will determine the type and age of subjects and the methodology to design, conduct, and interpret the study and its outcome.

- Affective testing includes acceptance/preference testing. Typical questions addressed are "which sample do you prefer," "how much do you like it," and "what don't you like."
- Analytical testing requires the use of objective sensory methodologies aiming to determine the characteristics/properties of the test item, without defining acceptance/preference measures. Analytical testing answers questions such as "which sample is more bitter" or "which sample is different." Analytical methods help define the sensory properties of the medicinal product preparation and differentiate between variants but will not directly predict how much a variant will be liked. It is often used as a technical tool to support development/optimization purposes.
- Ranking is a very straightforward method that can be used for preference or analytical assessment ("please rank samples in order of your personal preference" or "please rank samples in increasing order of bitterness," respectively). The advantage of this method is its simple procedure. However, the study results may be biased due to limited memory and attention of the tester during the entire testing period. This limitation may be more pronounced depending on the age of the subjects participating.

Evaluation principles

In most cases smell, texture, taste, and aftertaste, and sometimes also appearance (e.g., if colored) are addressed. The language used in the questionnaire must be simple, intelligible, and plain for all

participants independent of their age, social skills, and developmental level. It is recommended to utilize commonly used terms relevant to the age of the participants to describe these properties:

- Sweet, salty, sour, and bitter characterizing the taste
- Thin, thick, viscous, gritty aiming to portray the texture of the testing item
- Sweet, salty, sour, and bitter but also astringent, numbness, or freshness for the aftertaste

The following two principles for taste evaluation are established in palatability studies with children: verbal judgment and facial hedonic scale.

- Verbal judgement followed by scoring in a scale of (i.e., 1–5, with a score of 1 corresponding to very good and a score of 5 to very bad) facilitates the statistical evaluation of the data obtained.
- The facial hedonic scale allows the expression of preferences using a pictorial scale.

Children below 5–6 years are not considered able to express differences in taste perception by use of the preferential method. A reliable estimation of differences particularly in this age group (< 5 years) might be achieved using the child's own spontaneous verbal judgements following a control question. The facial hedonic scale cannot be used solely to discriminate between the tastes of tested formulations in the youngest age group. Young children may link the figures with things other than taste (e.g., happy face = I will not stay longer in hospital, sad face = pain or discomfort). Facial expressions and behavior pattern of the subject itself (wry faces, shrugging shoulders, vomiting, or spitting the formulation out) may also reflect the acceptance of the tested formulation. To assure a reliable outcome from a palatability study with young children, it is suggested to involve parents, guardians, or health providers in the study, asking about any discomfort or other observations in relation to the acceptance of the study medicine. Since older children judge more critically than younger ones, they are able to discriminate between the formulations using both the verbal judgment and hedonic scale.

Independent of the age of the children and the evaluation principle selected, it is suggested to include in the questionnaire concluding questions to the overall taste evaluation of the formulation such as "which formulation was the best" or "which formulation tasted worst." Similar approaches may be followed for the assessment of the flavor used: "which of the tested flavors did you like the most" or "which one did you dislike the most."

ORAL REHYDRATION

SOLUTION

GENERAL PRODUCT INFORMATION

Oral rehydration solution (ORS) is an oral powder–containing mixture of glucose sodium chloride, potassium chloride, and sodium citrate. After being dissolved in the requisite volume of water, it is used for the prevention and treatment of dehydration due to diarrhea, including maintenance therapy.

ORS and zinc are recommended by the WHO and UNICEF to be used collectively to ensure the effective treatment of diarrhea.[1,2] ORS replaces the essential fluids and salts lost through diarrhea. Zinc decreases the duration and severity of an episode and reduces the risk of recurrence in the immediate short term. ORS and zinc are highly effective and affordable products for treatment of childhood diarrhea that could prevent deaths in up to 93% of diarrhea cases.

ORS is included in WHO's Essential Medicines List, and Priority Medicines for Mothers and Children, as well as national EMLs and treatment guidelines for childhood diarrhea treatment in many high-burden countries. ORS is also listed as a lifesaving commodity identified and targeted for scale-up and access by the UN Commission on Life-Saving Commodities for Women and Children.

Note: In 2005, WHO and UNICEF recommended a switch from the standard ORS to an improved lower-osmolarity formulation, to be combined with zinc supplementation.

[1] World Health Organization. 2005. The Treatment of Diarrhea: A Manual for Physicians and other Senior Health Workers. Geneva: WHO. Available at https://apps.who.int/iris/handle/10665/43209

[2] World Health Organization. 2006. Implementing the New Recommendations on the Clinical Management of Diarrhea: Guidelines for Policy Makers and Programme Managers. Geneva: WHO. Available at https://apps.who.int/iris/handle/10665/43456?locale-attribute=es&

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by UNICEF and those with a proven record of quality products.

2. Procure only ORS that is manufactured as a pharmaceutical product following all GMP requirements. ORS is considered a medicine by inclusion in the WHO EML; therefore, procurement should be based on product quality.

3. Procurers need to focus on product quality to ensure that it is safe for patient use.

KEY QUALITY CONSIDERATIONS

Product specification

ORS that is procured should have a product composition in line with that described in the "Product Specification" section below. WHO and UNICEF currently recommend the use of low-osmolarity ORS with a total osmolarity of 245 mOsm/L due to its greater effectiveness, instead of the previous standard ORS with a total osmolarity of 311 mOsm/L.

ORS that is procured should contain only four ingredients: glucose, sodium chloride, potassium chloride, and trisodium citrate, in the concentrations described in the "Product Specification" section below. The addition of other ingredients, such as other minerals (especially zinc) or vitamins, has not been shown to improve the solution's efficacy. For this reason, neither UNICEF nor WHO approve or provide ORS with additives for use in the treatment of the childhood diarrhea. Any additional ingredients should be clearly described on the packet. Manufacturers must demonstrate their clinical value, safety, and chemical stability.

Packaging and labeling

ORS should be packaged in multi-ply, laminated, aluminum foil sachets, as the product can be affected by highly humid environmental conditions. A combination of polyethylene (inside), aluminum (middle), and polyester or any other suitable coating compound (outside) has proven to be satisfactory for packing ORS. However, product stability also depends on these conditions: the raw material must be dry, the sealing must be perfect, and the final product must be stored appropriately.

ORS should be procured with packaging designated with: (1) the total net mass and the mass of the contents of each constituent ingredient, both expressed in grams; (2) the required volume of water to reconstitute the solution; (3) directions for the preparation of the solution and its administration; and (4) a warning that any solution that remains unused 24 hours after preparation is to be discarded.

Storage, transportation, and distribution

ORS is stable at room temperature and does not require cold chain storage.

Name of the Medicinal Product

Low-osmolarity oral rehydration salts

Pharmaceutical Form

Oral powder

A white, crystalline powder; odorless

Note: The recommended formulations of ORS can be produced in three dosage forms: powder, tablet, and liquid. This document deals only with the production of ORS in powder form, which is the dosage form on the WHO EML.

Qualitative and Quantitative Composition

Product Composition of ORS

COMPONENT	CHEMICAL FORMULA	CONCENTRATION (g/L)
Sodium chloride	NaCl	2.6
Glucose anhydrous	$C_6H_{12}O_6$	13.5
Potassium chloride	KCl	1.5
Trisodium citrate, dihydrate	$C_6H_5Na_3O_7,2H_2O$	2.9

Concentrations Yielded from Dissolution in Drinking Water

COMPONENT	CONCENTRATION
Sodium	75 mmol/L
Chloride	65 mmol/L
Glucose, anhydrous	75 mmol/L
Potassium	20 mmol/L
Citrate	10 mmol/L

Total osmolarity: 245 mOsm/L

This ORS composition has passed extensive clinical evaluations and stability tests. The pharmacokinetics and therapeutic values of the substances are as follows:

– Glucose facilitates the absorption of sodium (and hence water) on a 1:1 molar basis in the small intestine.

– Sodium and potassium are needed to replace the losses of these essential ions during diarrhea (and vomiting).

– Citrate corrects the acidosis that occurs as a result of diarrhea and dehydration.

ORS may contain suitable pharmaceutical aids (e.g., suitable flow agent in minimal quantities to improve the flow characteristics) and/or the flavoring agents.

Some papers describe that a number of mild to moderately dehydrated children refuse to drink ORS because of its strong salty taste.[3] The WHO Control of Diarrhoeal Diseases (CDD) Programme conducted a safety/efficacy study in Egypt and an acceptability study in the Philippines of flavored and colored ORS solutions.[4] The results of these studies showed

[3] Loo, D. M. 1., F. van der Graaf, and W. T. Ten. 2004. "The Effect of Flavoring Oral Rehydration Solution on Its Composition and Palatability." J Pediatric Gastroenterology and Nutrition 39(5):545–8.

[4] Available at: http://apps.who.int/iris/bitstream/handle/10665/69227/WHO_FCH_CAH_06.1.pdf;jsessionid=A426B006186DD09F4F593604F6D66435?sequence=1

neither an advantage nor disadvantage for the flavored and colored ORS when compared to the standard ORS with regard to safety, acceptability, and correct use. For this reason, and with the aim of making an essential drug available at low price in the public health system, UNICEF and WHO recommend that governments use the ORS composition that contains only the four basic ingredients needed to effectively treat dehydration due to diarrhea. ORS produced for use in the private sector (commercial sales) and indicated for the prevention and treatment of dehydration due to diarrhea, may contain flavoring or coloring agents. In practice, two or more types of flavoring are often needed, and saccharine is added to increase their effect. The ingredients used for flavoring ORS must be among those listed as "generally recognized as safe" for their intended use by the US Food and Drug Administration (FDA) or by the US Flavor Extract Manufacturer's Association. The responsibility for demonstrating the clinical efficacy, safety, and chemical stability of such products remains with the manufacturer.

Packaging and Presentation

ORS is a powder for dilution in 200 mL, 500 mL, and 1 L. Products are packed in hermetically sealed, laminated sachets. The sachets may be made of multi-ply laminations with aluminum foil or polyethylene foil.

The multi-ply laminated aluminum foil sachet is usually recommended for ORS. A combination of polyethylene (inside), aluminum (middle), and polyester or any other suitable coating compound (outside) has proven to be satisfactory for packing ORS.

The packaging configurations for ORS procured by UNICEF are:
- ORS low osmolarity, 20.5 g/1 L
- ORS low osmolarity, 10.2 g/0.5 L

ORS and zinc are recommended by WHO for combination use to ensure the effective treatment of diarrhea; to improve compliance, a co-package of ORS and zinc in accordance with WHO treatment protocol guidelines is offered by some manufacturers to improve treatment regimen adherence.

The packaging configurations for ORS procured by UNICEF are:
- ORS low osmolarity, 2 sachets for 1 L + zinc 20-mg dispersible tablets, blister pack of 10, packed together in a kit
- ORS low osmolarity, 4 sachets for 0.5 L + zinc 20-mg dispersible tablets, blister pack of 10, packed together in a kit

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment, as described in Module II.

WHO-prequalified products

ORS is not included in the WHO PQP. Therefore, no WHO-prequalified ORS products are available.

SRA-approved products

As of June 2022, there are no ORS products approved in SRA countries in the same formulation and strength as that described in the "Product Specifications" section.[5]

When manufacturers claim that products are approved by an SRA, they should provide the following information/documents to verify the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP (including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information) will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects manufacturers among GMP approved manufacturers via tenders (UNICEF contract awards) to supply products usually over a two- or three-year period.[6] The manufacturer KBI (Germany) is listed by UNICEF as a contract award in the 2020 list to supply ORS and zinc tablets co-pack, with an exceptional extension of 12 months. The lists from 2021 and January, February and March 2022 did not include ORS products.

It is recommended to check the UNICEF website for updated information at the time of procurement.

Related products

ORS products approved in the UK[7] contain glucose monohydrate 17.9 g/L, sodium chloride 2.35 g/L, potassium chloride 1.5 g/L, sodium citrate dihydrate 1.95 g/L, and citric acid anhydrous 0.64 g/L. They are available in sachets of 200 mL. When dissolved in 200 mL of water, each ORS sachet will

[5] The ORS products approved in SRA countries are of different formulations and strengths. Furthermore, ORS is considered to be an over-the-counter medicine, which some SRAs do not include in the databases of approved drugs published on their websites, making it difficult to find SRA-approved ORS products.
[6] Available at: https://www.unicef.org/supply/contract-awards
[7] Available at: https://mhraproducts4853.blob.core.windows.net/docs/ed1a0141ce05d6892a9875cdf3041fdb3dea451d https://mhraproducts4853.blob.core.windows.net/docs/f269fe360f70ea8b2f71ffdb9ae64ea23933da6e

give the equivalent of: glucose 90 mmol/L, sodium 60 mmol/L, potassium 20 mmol/L, chloride 60 mmol/L, and citrate 10 mmol/L.

ORS products approved in Australia[8] contain glucose monohydrate 17.8 g/L, sodium chloride 2.35 g/L, potassium chloride 1.5 g/L, and sodium acid citrate 2.65 g/L. They are available in sachets of 200 mL. When dissolved in 200 mL of water, each ORS sachet will give the equivalent of: glucose 90 mmol/L, sodium 63 mmol/L, potassium 20 mmol/L, chloride 60 mmol/L, and citrate 11 mmol/L.

Although the ORS formulation in the "Product Specification" section below is recommended, the above formulations approved in the UK and Australia also meet the WHO and UNICEF's criteria for acceptable ORS formulations.[9] These criteria are listed below; they refer to the desired characteristics of the solution after it has been prepared according to the instructions on the packet:

- Total substance concentration (including that contributed by glucose) should be within the range of 200–310 mmol/L.
- Individual substance concentration:
  - Glucose should at least equal that of sodium but should not exceed 111 mmol/L.
  - Sodium should be within the range of 60–-90 mEq/ or mmol/L.
  - Potassium should be within the range of 15–25 mEq/ or mmol/L.
  - Citrate should be within the range of 8–12 mmol/L.
  - Chloride should be within the range of 50–80 mEq/ or mmol/L.

Other formulations of ORS that exist in the market include:

ORS-hydrogen carbonate (bicarbonate)

- Trisodium citrate dihydrate may be replaced by 2.5 g/L of sodium hydrogen carbonate, $NaHCO_3$ (sodium bicarbonate). However, as the stability of the latter formulation under tropical conditions is very poor, it is recommended only in ORS manufactured for immediate use, or where sodium hydrogen carbonate is packaged in separate packets.
- This formulation would also allow the use of 14.85 g/L of glucose monohydrate, $C_6H_{12}O_6,H_2O$, instead of anhydrous glucose.
- The title of the two formulations could be distinguished by: "ORS-citrate" or "ORS-hydrogen carbonate" (bicarbonate). The title ORS used without qualification implies the product is the citrate formulation.

STORAGE, STABILITY, AND DEGRADATION

ORS containing citrate (as opposed to bicarbonate containing ORS) is stable at ambient temperatures/humidity and is unlikely to undergo any significant degradation from heat/humidity if it is properly manufactured, packaged, and sealed.

[8] ARTG ID 199575 available at https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=772D9ABAE6D8E787CA2588550043BE8B&agid=(PrintDetailsPublic)&actionid=1
ARTG ID 81381 available at https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=002F426497D428AECA2588550043D37F&agid=(PrintDetailsPublic)&actionid=1

[9] World Health Organization. 2002. "New Formula Oral Rehydration Solution." In WHO Drug Information. Vol. 16, No. Geneva: WHO.

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: ORS should be kept in a sealed packet; if a free-flowing powder is required, it should be kept in an airtight packet, preferably made of aluminum laminate. The USP monograph for ORS recommends preservation in a tight container and avoiding exposure to temperatures exceeding 30°C.

ORS does not need to be maintained in the cold chain.

Discard any solution that remains unused 24 hours after preparation.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the International Pharmacopeia, US Pharmacopeia, and British Pharmacopeia, depending on the quality assurance policy of the procurement agency or the equivalent thereof.

The testing parameters and acceptance criteria of the pharmacopeias are similar. USP and BP monographs are applicable for ORS formulations containing sodium bicarbonate or sodium citrate, whereas International Pharmacopeia is applicable only for ORS formulations containing trisodium citrate.

Table ORS-63. International Pharmacopeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Sugar	Melts when heated; first becomes yellow then brown, swells up and burns, evolving an odor of burnt sugar.	As per IP monograph of ORS
b) Sodium	The test solution yields reaction A described under 2.1 General identification tests as characteristic of sodium.	2.1 General identification tests
c) Potassium	A yellow-orange precipitate is produced.	As per IP monograph of ORS
d) Chlorides	A 5-mL aliquot of the test solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.	2.1 General identification tests
e) Citrates	A 5-mL aliquot of the test solution after neutralization yields reaction A described under 2.1 General identification tests as characteristic of citrates.	2.1 General identification tests
f) Glucose	A copious red precipitate is produced (glucose).	As per IP monograph of ORS
Uniformity of mass	Not more than two of the individual masses of the 20 packets deviate from the average mass by more than 5% and none deviates by more than 10%.	As per IP monograph of ORS
Loss on drying	At 50°C it loses not more than 20 mg/g.	As per IP monograph of ORS
pH of the reconstituted solution	7.0–8.8	As per IP monograph of ORS
Assay a) Sodium	90–110%	1.8 Atomic spectrometry: emission and absorption
b) Potassium	90–110%	1.8 Atomic spectrometry: emission and absorption

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
c) Chloride	90–110%	Titration, as per IP monograph of ORS
d) Citrate	90–110%	2.6 Non-aqueous titration, Method A
e) Glucose	90–110%	Optical rotation, as per IP monograph of ORS

Table ORS-64. US Pharmacopeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Sodium	The sample imparts an intense yellow color to a nonluminous flame.	As per USP Monograph of ORS
b) Potassium	The sample imparts a violet color to a nonluminous flame. Since the presence of small quantities of sodium masks the color, screen out the yellow color produced by sodium by viewing through a blue filter that blocks the emission at 589 nm (sodium), but is transparent to emission at 404 nm (potassium).	As per USP Monograph of ORS
c) Chloride	Meet the requirements.	USP<191>
d) Bicarbonate (if present)	Where it contains sodium bicarbonate, it dissolves with effervescence, and the collected gas so obtained meets the requirements.	USP<191>
e) Citrate	Where it contains sodium citrate, it meets the requirements.	USP<191>
f) Dextrose (Glucose)	Where it contains dextrose, a copious red precipitate of cuprous oxide is formed.	As per USP monograph of ORS
Assay a) Dextrose	90–110%	USP<781A>, Angular rotation
b) Sodium and Potassium	90–110%	Photometry, as per USP monograph of ORS
c) Chloride	90–110%	Titration, as per USP monograph of ORS
d) Bicarbonate (if present)	90–110%	Titration, as per USP monograph of ORS
e) Citrate (if present)	90–110%	USP<345>, Assay for citric acid/citrate and phosphate

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Minimum Fill	The average net weight of the contents of the 10 containers is no less than (NLT) the labeled amount, and the net weight of the contents of any single container is NLT 95% and not more than (NMT) 105% of the labeled amount. If the contents of NMT one container are less than 95% but NLT 90% of the labeled amount, or more than 105% but NMT 110% of the labeled amount, determine the net weight of the contents of 20 additional containers. The average net weight of the contents of 30 containers is NLT the labeled amount, and the net weight of the contents of NMT one of the 30 containers is less than 95% but NLT 90% of the labeled amount, or more than 105% but NMT 110% of the labeled amount.	USP<755>
pH of the reconstituted solution	7.0–8.8	USP<791>
Loss on drying	At 50°C, NMT 1.0%	USP<731>

Table ORS-65. British Pharmacopeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Glucose	When heated with cupri-tartaric solution R1 a copious precipitate of copper (i) oxide is produced.	As per BP monograph of ORS
b) Potassium	Yields reaction B characteristic of potassium salts.	Appendix VI
c) Sodium	Yields reaction A characteristic of sodium salts.	Appendix VI
d) Chlorides	Yields reaction A characteristic of chloride salts.	Appendix VI
e) Citrates (if present)	Yields reactions A and B characteristic of citrates.	Appendix VI
f) Sodium bicarbonate (if present)	Vigorous effervescence is produced.	As per BP monograph of ORS
Assay a) Sodium	90–110%	Appendix II D
b) Potassium	90–110%	Appendix II D
c) Chloride	90–110%	Titration, as per BP monograph of ORS
d) Citrate (if present)	90–110%	Appendix VIII A
e) Bicarbonate (if present)	90–110%	Titration, as per BP monograph of ORS
f) Glucose	90–110%	Appendix V F
Uniformity of mass	Meet the requirements	EP 2.9.5

Additional tests for the ORS products as recommended by WHO are listed below:

Seal (only if packed in aluminum laminate)

As an in-process control test during packaging, check 10 packets every 10–20 minutes.

Bundle up the packets and submerge them underwater in a vacuum desiccator or equivalent device. Draw a vacuum of about 18kPa (15 cm of mercury or -0.8 bar) and hold for one minute. Examine for air leakage indicated by a fine stream of bubbles. Reestablish normal pressure and open packets to examine for water penetration.

If water penetration (leakage) is observed, search for the reason (e.g. dirty sealing jaws, wrinkles, pinholes in laminate, product sealed with laminate), and reject the batch if necessary.

Appearance of product

A white, crystalline powder, odorless.

Appearance of solution

Dissolve the entire contents of one packet of ORS or about 20.5 g of the mixture in 1,000 mL of water.

The solution should be clear and odorless, or should have only a faint yellow stain.

ORAL REHYDRATION ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

ORS is indicated for the treatment of diarrhea and fluid loss due to diarrhea in infants, children, and adults.

Posology, method, and duration of administration

The amount of ORS solution needed for rehydration is calculated based on the child's weight. The amount of solution required also depends on the child's dehydration status. Children with more marked signs of dehydration or who continue to pass frequent watery stools will require more solution than those with less marked signs or who are not passing frequent stools. If a child wants more than the estimated amount of ORS solution, and there are no signs of overhydration, give more.

The approximate amount of ORS solution to give in the first 4 hours based on the child's weight:

- Below 4 months / less than 5 kg: 200–400 mL
- 4–11 months / 5–7.9 kg: 400–600 mL
- 12–23 months / 8–10.9 kg: 600–800 mL
- To 4 years / 11–15.9 kg: 800–1,200 mL
- To 14 years / 16–29.9 kg: 1,200–2,200 mL
- 15 years or older / 30 kg or more: 2,200–4,000 mL

Notes

Use the patient's age only when the weight is not known. The amount may also be estimated by multiplying the child's weight in kg times 75 mL.

During the initial stages of therapy, while still dehydrated, adults can consume up to 750 mL per hour, if necessary, and children up to 20 mL/kg body weight per hour.

Normal feeding can continue after the initial fluid deficit has been corrected. Breastfeeding should continue between administrations of ORS.

Edematous (puffy) eyelids are a sign of overhydration. If this occurs, stop giving ORS solution, but give breast milk or plain water, and food. Do not give a diuretic. When the edema has gone, resume giving ORS solution or home fluids according to Treatment Plan A from WHO (http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf).

After 4 hours, reassess the child fully. Then decide what treatment to give next:

- If signs of severe dehydration have appeared, IV therapy should be started following WHO Treatment Plan C (http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf). This is very unusual, however, occurring only in children who drink ORS solution poorly and pass large watery stools frequently during the rehydration period.
- If the child still has signs indicating some dehydration, continue oral rehydration therapy by repeating the treatment described above. At the same time, start to offer food, milk and other fluids, as described in WHO Treatment Plan A (http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf), and continue to reassess the child frequently.
- If there are no signs of dehydration, the child should be considered fully rehydrated.

Contraindications

ORS is contraindicated in patients exhibiting the following conditions: cirrhosis of the liver, congestive cardiac failure, nephrotic syndrome, acute and chronic renal failure, ischemic heart disease, adrenocortical insufficiency, hyperkalemic periodic paralysis, hyperkalemia, hypoventilatory states, chloride depletion due to continuous gastric fluid loss, metabolic or respiratory alkalosis, hypocalcemia, hyperosmolar states in anuria or oliguria, edematous sodium retaining conditions, hypertension, peripheral or pulmonary edema or toxemia of pregnancy, severe vomiting, diarrhea and dehydration requiring fluid therapy, dextrose malabsorption, diabetes mellitus, thiamine deficiency, severe undernutrition, hemodilution, hypophosphatemia, sepsis, and trauma.

ORS is also contraindicated for use in patients undergoing treatment with the following: sodium-retaining drugs (e.g., corticosteroids, NSAIDs, carbenoxolone), or diuretics known to produce hypochloremic alkalosis.

Special warnings and precautions for use

Administer with care in cases of acute dehydration, heat cramps, extensive tissue destruction, or if patients are receiving potassium-sparing diuretics. Concurrent use with other potassium-containing drugs may precipitate hyperkalemia.

It is very important to dissolve ORS in water of the correct volume. A weak solution will not contain optimum glucose and electrolyte concentration and a strong solution may give rise to electrolyte imbalance. Diarrhea can have very serious consequences in children under 3 years old. Immediate medical advice should be sought. In other age groups, if symptoms persist for more than 24–48 hours, consult a doctor.

If nausea and vomiting are present with the diarrhea, small and frequent amounts of ORS should be drunk first. In infants, immediate medical assistance should be obtained. Use within 1 hour of reconstitution, or within 24 hours if stored in a refrigerator.

See also "Overdose" section below.

Interaction with other medicinal products and other forms of interaction

Sodium bicarbonate

Increases excretion of lithium, resulting in a reduced plasma-lithium concentration.

Potassium chloride

ACE inhibitors (hyperkalemia); cyclosporin (increased risk of hyperkalemia); potassium-sparing diuretics where hyperkalemia may result. No known interactions to other actives.

For more details, see also under "Contraindications" section.

Pregnancy and lactation

Use in patients with pre-eclampsia is contraindicated. The product should only be administered if the expected benefit to the mother is thought to outweigh any possible risk to the fetus or neonate.

Effects on ability to drive and use machines

ORS has no influence on the ability to drive or use machines.

Undesirable effects

The following adverse effects have been reported although more commonly following excessive amounts: hypernatremia, edema, nausea, vomiting, diarrhea, abdominal cramps, thirst, reduced salivation, lachrymation, sweating, fever, tachycardia, renal failure, respiratory arrest, headache, dizziness, restlessness, irritability, weakness, muscular twitching, coma, convulsions, hyperkalemia, gastrointestinal ulceration, metabolic alkalosis, muscle hypertonicity, flatulence, dehydration, and raised blood pressure.

Overdose

Iso-osmotic overload is managed by restricting sodium, potassium, and water intake plus measures to increase renal sodium, potassium and water output by using "loop diuretics" (e.g., frusemide).

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT[1]

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of ORS products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on ORS.

Raw materials (key ingredients)

Glucose

The use of glucose for the preparation of ORS does not require a pyrogen-free, pharmaceutical grade such as that used for parenteral preparations. An "oral grade" quality is therefore fully acceptable, provided that the quality is within the limits set in the pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If such a quality is not available, or the limits set in the specifications prove to be a serious constraint for the establishment of local production and the provision of ORS in general, the food standard may be adopted.

Only anhydrous glucose is recommended. Contact of glucose monohydrate with trisodium citrate and prolonged exposure to tropical (hot and humid) conditions can lead to liquefaction of the whole mixture.

Whenever appropriate facilities for microbiological control are available, it is recommended that the microbiological purity of the glucose be checked.

Sodium chloride

The pharmaceutical grade is recommended and the specifications should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium chloride is produced locally, but is not of the mentioned pharmaceutical grade, a standard for a food grade quality may be applied.

Potassium chloride

The pharmaceutical grade is recommended and the specifications should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium chloride is produced locally, but is not of the mentioned pharmaceutical grade, a standard for a food grade quality may be applied.

[1] World Health Organization. 2006. Oral Rehydration Salts: Production of the New ORS. WHO: Geneva. Available at http://apps.who.int/iris/bitstream/10665/69227/1/WHO_FCH_CAH_06.1.pdf.

Sodium citrate

To achieve the required pH limits in the ORS solution, only trisodium citrate is indicated.

The recommended ORS-citrate composition contains trisodium citrate dihydrate as this form is more widely available on the market and produced in large quantities. Anhydrous trisodium citrate can, however, be used without hesitation where such a quality is available and preferred, but a higher price (by about 40%) must be expected.

Stability tests have shown that a combination of glucose monohydrate and trisodium citrate dihydrate is far less stable, and the high total content of water crystallization in both ingredients eventually leads to liquefaction if packed in polyethylene and exposed to tropical conditions (23–40°C and 82–92%RH). Therefore, such combination should be avoided.

The pharmaceutical grade is recommended and the specifications should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium citrate is produced locally, but is not of the mentioned pharmaceutical grade, the food grade standard may be applied.

Manufacturers of these key ingredients should provide evidence for GMP compliance. However, the key ingredients are atypical APIs, meaning that the manufacturing process and controls are not typically designed to meet API GMPs. As an alternative, there should be a clear specification; the site should have been audited, changes should be controlled, and appropriate checks should be made on incoming goods.

Other ingredients

With the aim of making an essential medicine available at an affordable price in the public health system, the recommended composition should contain only the four basic ingredients (glucose, sodium chloride, potassium chloride, and trisodium citrate) in the concentrations described in this document for preparing an effective (clinically tested) ORS.

Excipients such as colloidal silicon dioxide (Aerosil®) improve the flow characteristics but do not dissolve in the solution and render it turbid. Their use is normally only indicated when automatic packaging equipment is used, and only recommended if the flow properties of the available raw materials hamper accurate dosing and proper functioning of the equipment.

ORS may contain flavoring or coloring agents if this is seen as vital by a manufacturer for promoting the product or to compete with other brands. In practice, two or more types of flavoring are often needed, and saccharine is added to increase their effect. The ingredients used for flavoring ORS must be among those listed as "generally recognized as safe" for their intended use by the US FDA or by the US Flavor Extract Manufacturer's Association. The responsibility for demonstrating the clinical efficacy, safety, and chemical stability of such products remains with the manufacturer.

Manufacturing process

ORS is a straightforward product to manufacture, but some specific procedures should be observed to ensure the quality of the product. Recommendations and technical procedures that should be considered during the manufacture of ORS include the following:

- After prolonged storage in hot and humid climates, the raw materials may have absorbed a substantial amount of moisture and have a water content higher than the indicated limit of 1%. The use of such ingredients for the manufacture of ORS may result in accelerated decomposition. Therefore, if a raw material containing water exceeding the indicated limit is to be used, it is preferable to dry it at the recommended temperature as follows: glucose, anhydrous at max. 105°C; sodium chloride, potassium chloride, and trisodium citrate at max. 130°C.

The time required for drying to the specified limit depends on the amount of water absorbed but should not exceed 16 hours (overnight). In tropical countries, special attention must be given to the temperature and relative humidity of the air to be used for drying. It is therefore important to compare the moisture content in the raw material before and after the drying process to ascertain the extent of water loss during drying (efficacy of drying). The condition of the intake of air is less critical in countries with a cold and dry climate.

Dried material should not be exposed to high humidity and heat after it has been taken out of the dryer. It is therefore advisable to install the drying equipment in a controlled, air-conditioned room where the dried material can be filled into airtight drums and safely stored until required for use.

- However, whenever possible, drying should be avoided. This can be done by ordering raw materials with a specified low water content, or by placing orders at intervals so that the goods are fresh when used, and by storing them in such a way that they are protected from humidity and other possible negative influences.
- All four ingredients should be of the same medium or fine crystalline grade (below 1,000 microns). This requirement can be specified when the ingredients are ordered, however, it is often difficult to obtain. Therefore, occasionally milling, grinding, or sifting to the required uniform particle size may be required to obtain a uniform particle size. This is important for uniform mixing of the product.
- Weighing of ingredients should be done only when they are ready for mixing—that is, after drying, grating, and sieving.
- During ORS blending, particularly in tropical countries, the following points should be noted:
  - Glucose, with its abrasive characteristics and especially when it is in fine powder form, may enter into the mechanical parts and damage shaft seals and gaskets; it may even cause the product to become contaminated with fine particles from the seals. In such case, the ordinary shaft seals should be replaced by air-purged seals, using compressed air (oil-free and dry).
  - ORS has a tendency to caramelize rapidly in humidity and heat, therefore almost daily cleaning of the mixing machine is required.
- Depending on the quality of the raw materials, particularly glucose, the handling of ORS on automatic filling/dosing equipment is normally accompanied by the development of dust, which can negatively influence the sealing operation. The intensity of dust formation is directly linked to the speed of the machine. A higher output can be achieved only if all the ingredients in the ORS mixer are of a dust-free, uniform medium crystalline or if they are granular in size, which guarantees an easy flow.

- Intentional excess filling/dosing to compensate for any product that might remain in the packet at the time of use should be strictly avoided as it may result in a higher sodium concentration in the solution and ultimately lead to hypernatremia, particularly in infants.

Notes:

- *The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[2, 3]

Packaging

The kind of packaging material to be used for ORS depends mainly on the required standard of stability, the climatic conditions, and the available resources.

Multi-ply laminations with aluminum foil

This type of packaging is usually recommended for ORS. This type of packaging material is available in numerous different combinations of compounds. A combination of polyethylene, aluminum, and polyester (or any other suitable coating compound) has proved to be satisfactory for packing ORS. The polyethylene on the inner side is essential for heat-sealing the compound together; the aluminum in the middle reduces the permeability to gas and steam (so that it is no longer effectively measurable); and the polyester on the outside protects the aluminum, the ink on the aluminum, and improves the mechanical qualities in general.

For recommended ORS compositions, the thickness should, whenever possible, be selected within the following limits:

- Inside: polyethylene (PE) 0.040–0.050 mm or 36.9–46.1 g/m^2
- Middle: aluminum (ALU) 0.009–0.015 mm or 24.3–40.5 g/m^2
- Outside: polyester (P) 0.012–0.015 mm or 12.9–20.9 g/m^2

Choice of the recommended compound does not guarantee a stable and satisfactory product if the raw material is not dry, the sealing is imperfect, or if the final product is not stored appropriately.

Polyethylene foil

ORS can in certain cases be perfectly well packed in transparent or printed polyethylene (low density), which in fact offers a particular advantage in dry and hot climates. In such conditions, the evaporating water of crystallization in the raw material can escape through the pores of the foil and thus the moisture content of the product is reduced. In hot and humid climates, however, the reaction may be the reverse, and the moisture may penetrate through the pores into the packet, where it is absorbed by the mixture, causing lumping or even deterioration.

[2] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[3] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

ORS-citrate does not absolutely require an impermeable packaging material. If packed in polyethylene it may, however, absorb moisture and have some lumping, which is usually acceptable.

The possibilities for the use of polyethylene packets are as follows:

- Use of a single polyethylene bag for the whole ORS mixture, with the composition, instructions, brand, and other information printed on the polyethylene
- Use of two unprinted polyethylene bags, one for the whole ORS mixture and a second to hold together the first bag containing ORS and a printed insert (with composition, instructions for use, illustrations, etc.).

Suitable sizes for these packets and the minimal gauges of polyethylene recommended for each are as follows:

- Inner bag containing glucose, sodium chloride, potassium chloride, and trisodium citrate with min. 0.04-mm gauge of PE and size 65 mm x 100 mm.
- Outer bag holding ORS and label with min. 05-mm gauge of PE and size 70 mm x 120 mm.

Bioequivalence requirements

Not applicable.

ZINC

SULFATE, GLUCONATE, ACETATE, AND CITRATE
DISPERSIBLE TABLETS 10 MG, 20 MG
ORAL SOLUTION 10 MG PER UNIT DOSAGE

GENERAL PRODUCT INFORMATION

The use of zinc supplements in addition to ORS is recommended by WHO and UNICEF in the management of acute diarrhea in children.[1,2] Zinc is also considered to be a lifesaving drug by the UN Commission on Life-Saving Commodities for Women and Children.

Zinc in zinc supplements can be in the form of zinc sulfate, zinc gluconate, zinc acetate, or zinc citrate, all water-soluble zinc salts. The most widely used zinc salt is zinc sulfate, primarily because it is the cheapest of the four zinc salts mentioned above. Clinical trials that have evaluated the efficacy of zinc supplements in the management of diarrhea have used different zinc salts, and no difference in efficacy and safety has been shown. Therefore, all are considered acceptable. However, because zinc sulfate is the most widely used zinc salt, this document focuses on zinc products containing zinc sulfate. Zinc sulfate is also included in the WHO Model List of Essential Medicines.

Zinc supplements for administration to children can take the form of dispersible tablets or oral solution (syrup). However, because the burden of diarrheal disease is in early childhood, especially among children less than 2 years of age, dispersible tablets are the preferred formulation for ease of administration and logistics.

A strong safety profile allows the potential classification of zinc as an over-the-counter drug, without requiring a prescription.

[1] WHO. 2005. The Treatment of Diarrhea: A Manual for Physicians and Other Senior Health Workers. Geneva: WHO. Available at https://apps.who.int/iris/handle/10665/43209

[2] WHO. 2006. Implementing the New Recommendations on the Clinical Management of Diarrhea: Guidelines for Policy Makers and Programme Managers. Geneva: WHO. Available at https://www.who.int/publications/i/item/9241594217

KEY CONSIDERATIONS IN PROCUREMENT

1. Procured products should contain only zinc as an active ingredient to support the effective prevention and treatment of diarrhea in children. Many vitamin products and other nutritional supplements containing zinc that are available commercially, do not have the recommended dosage of zinc. It is especially important not to use zinc formulations containing iron because iron may interfere with zinc absorption.

2. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO and those with a proven record of quality products. Zinc products must comply with the quality specifications as detailed in the "Product Specifications" module below.

3. Procurers need to focus on product quality to ensure that it is safe for patient use.

KEY QUALITY CONSIDERATIONS

Product specification

Zinc tablets should be procured only in dispersible form as treatment is intended for use in infants and young children. Tablets should disaggregate completely in less than 60 seconds in 5 mL of normal drinking water or breast milk. Therefore, zinc tablets must be tested for disintegration time according to the compendial monograph. Procurers should check the certificate of analysis for disintegration data.

Packaging and labeling

Procure only zinc dispersible tablets that are packaged in blisters as they are water sensitive. Zinc tablets packaged in bottles or other similar multidose containers should not be procured because they will be subjected to humidity each time the container is opened and may start to disintegrate.

Only one strength of tablets should be procured to avoid dosing errors. Zinc dispersible tablets may contain either 10 or 20 mg of zinc. If 10 mg zinc tablets are procured, it will mean that older children will have to take two tablets each day; if 20 mg zinc tablets are chosen, it will mean that for younger infants only one-half tablet will be given each day, and therefore the 20 mg zinc tablets will need to be scored to facilitate this. Data demonstrating the weight uniformity of tablet halves should be provided for 20 mg scored tablets.

For zinc oral solutions, a concentration of 10 mg of elemental zinc per 5 mL (per 1 teaspoon) should be procured, because it is difficult to accurately measure one-half teaspoon of solution. It means that infants younger than 6 months of age will receive 1 teaspoon, while older children will need 2 teaspoons of oral solution per day.

Note: The method by which parents and caregivers measure liquid medications for children has long been identified as potentially problematic. Measuring devices used to administer liquid medications have included a variety of implements, including household teaspoons, dosing cups, droppers, cylindrical spoons, and oral syringes. Despite the common use, it has been demonstrated that household teaspoons do not accurately measure the 5-mL volume intended in dosing medications. For this reason, the use of dispersible tablets is preferable once the final product contains the correct dosage for the patient.[3,4]

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify with manufacturers that there is satisfactory stability data to support shelf life and storage conditions.

Procurers need to verify the stability data to ensure that the zinc product has a shelf life of at least 2 years when stored at room temperature. Zinc oral solutions are less stable than tablet dosage forms; therefore, their shelf life may be shorter than the shelf life of tablets. In low- and middle-income countries, the proper storage of oral solutions can also be more difficult than the storage of tablets. When considering whether zinc oral solutions should be procured, cost must be considered. This includes not just the price of the product but also the cost of storage and transportation.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Additional information about the finished product storage requirements can be found in Section 3.

Other considerations

During the procurement process, procurers should review data about the acceptability study conducted by the manufacturer of the zinc tablets or oral solution. Adherence to the treatment regimen for 10–14 days is essential to ensure the full effect of zinc for the prevention and treatment of diarrhea. However, adherence to treatment can be obtained only if the zinc products are acceptable to infants and young children. A short guide on how to conduct an acceptability study is described in the Annex.

Procurers should ensure the candidate zinc products (tablets or oral solutions) have been evaluated for taste masking during the procurement process. Water-soluble zinc salts have a strong, bitter, metallic aftertaste, and children will refuse to take the medicine if the metallic aftertaste is not completely masked. Taste masking is often done by adding fruit flavors to the product. Added flavors or sweeteners must be common to the areas where the product will be used. Acceptance of the product first by mothers is critical to adherence to treatment by children. A short guide on how to evaluate the taste is described in the Annex.

[3] Johnson, A., and R. Meyers, 2016. "Evaluation of Measuring Devices Packaged With Prescription Oral Liquid Medications." Journal of Pediatric Pharmacology and Therapeutics 21(1): 75–80.
[4] Batchelor, H. K., and J. F. Marriott. 2015. "Formulations for Children: Problems and Solutions." British Journal of Clinical Pharmacology 79(3): 405–18.

Name of the Medicinal Product

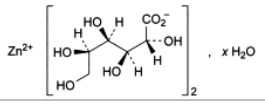
Zinc (sulfate, gluconate, acetate, citrate)

Chemical Name

ZINC PRODUCT	CHEMICAL NAME
Zinc sulfate*	Zinc sulfate monohydrate; Zinc sulfate heptahydrate
Zinc gluconate	Zinc bis(D-gluconate) hydrate; D-Gluconic acid, zinc salt, hydrate (2:1:?)
Zinc acetate	Zinc acetate dihydrate; Acetic acid, zinc salt, hydrate (2:1:2)
Zinc citrate	Zinc citrate; Trizinc dicitrate; Citric acid, zinc salt

**Zinc sulfate contains one or seven molecules of water. Zinc sulfate monohydrate is used in the manufacture of tablets, whereas the monohydrate or heptahydrate are used in the oral solution.*

Chemical Structure

ZINC PRODUCT	CHEMICAL STRUCTURE
Zinc sulfate	$ZnSO_4$, H_2O (monohydrate) $ZnSO_4$, $7H_2O$ (heptahydrate)
Zinc gluconate	$C_{12}H_{22}O_{14}Zn$; xH_2O 
Zinc acetate	$C_4H_6O_4Zn$; $2H_2O$ 
Zinc citrate	$C_{12}H_{10}O_{14}Zn_3$

Pharmaceutical Form

- Dispersible tablet
- Oral solution

Advantages of dispersible tablets versus oral solutions include:

- Easier to produce and production costs are less, which make them more affordable than standard liquid formulations
- More easily transportable and incurring lower handling and transportation costs for the same amount of active ingredient (less volume, less weight)
- Can be used in very young children (0–6 months)
- Can be dispersed in breast milk after pumping
- Easy to dispense and requiring minimal manipulation by health professionals and parents prior to use, which minimizes the risk of errors
- Requiring a small amount of water for administration

Qualitative and Quantitative Composition

Zinc sulfate dispersible tablet: Each tablet contains 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of elemental zinc.

List of typical excipients[5]:

- Aspartame
- Colloidal anhydrous silica
- Magnesium stearate
- Microcrystalline cellulose
- Crospovidone
- Maize starch

[5] Based on the formulation of the WHO-prequalified products.

	– Other sweeteners – Flavors Zinc sulfate oral solution: Each 5 mL contains 27.5 mg zinc sulfate monohydrate equivalent to 10 mg of elemental zinc.
Packaging and Presentation	Zinc dispersible tablets should be stored in blister packaging (usually available in PVC/PVDC-aluminum foil blister). Zinc oral solutions are packed in glass or plastic bottles. Oral solutions in multidose containers require a device capable of uniformly dispensing the required range of doses (5–10 mL for 10 mg/5 mL solution). WHO guidelines for the treatment of diarrhea recommend that zinc (10–20 mg/day) be given for 10–14 days to all children with diarrhea. Therefore, zinc tablets and oral solution should be packaged in quantities sufficient to provide a full treatment of 10–14 daily doses of zinc (e.g., at least 14 tablets per blister packaging or 140 mL as oral solution). WHO recommends using zinc and ORS together to ensure the effective treatment of diarrhea; a co-package of ORS and zinc in accordance with WHO treatment protocol guidelines is offered by some manufacturers to improve treatment regimen adherence. The packaging configurations procured by UNICEF are: – ORS low osmolarity, 2 sachets for 1 L + zinc 20 mg dispersible tablets, blister of 10, packed together in a kit – ORS low osmolarity, 4 sachets for 0.5 L + zinc 20 mg dispersible tablets, blister of 10, packed together in a kit.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

As of June 2022, there are four zinc sulfate products prequalified by the WHO PQP, as shown below. All of them are in the dispersible tablet dosage form. It is recommended to check the updated information at the time of procurement, which can be found at https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

Table Z-66. Examples of WHO-PQP Zinc Dispersible Tablet Dosage Form

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
DI002	Nutriset, BP 35, le Bois Ricard, Malaunay, 76770, France	FPP manufacturing site: Laboratoires Pharmaceutiques Rodael, 1 route de SOCX, Bierne, 59380, France	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC: 10 x 10's	4-Dec-12	36 months	Do not store above 30°C, protect from moisture.
		API manufacturing site: Dr Paul Lohmann GmbH KG, Haupstrasse 2, Emmerthal, 31860, Germany					
DI005	Macleods Pharmaceuticals Ltd, 304 Atlanta Arcade, Marol Church Road, Anheri-Kurla Road, Andheri (E), Mumbai, 400 059, India	FPP manufacturing site: Macleods Pharmaceuticals Ltd, Block No. N2, Village Theda, P.O. Lodhi Majra, Tehsil Baddi, District Solan, Himachal Pradesh, 174 101, India	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC: 10 x 10's	7-Dec-16	48 months	Do not store above 30°C, protect from light and moisture.
		API manufacturing site: Dr Paul Lohmann GmbH KG, Haupstrasse 2, 31860 Emmerthal, Germany;					
		Canton Laboratories Pvt Ltd, Survey No. 350, Mujpur, Taluka: Padra, Vadodara, Gujarat, 391440, India					
DI011	Ipca Laboratories Ltd, 48 Kandivli Industrial Estate, Kandivli (West), Mumbai, Maharashtra, 400 067, India	FPP manufacturing site: Ipca Laboratories Ltd, Plot No 255/1, Village Athal, Silvassa, Dadra & Nagar Haveli (Union Territory), 396 230, India	Tablet, dispersible 20 mg	Blister Alu-PVdC/PVC: 10 x 10's Blister strip Alu-Alu	25-May-20	Alu-PVdC/PVC blister: 24 months	Do not store above 30°C, protect from moisture.

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
		API manufacturing site: Dr Paul Lohmann GmbH KG, Haupstrasse 2, Emmerthal, 31860, Germany		10 x 10's		Alu-Alu blister: 36 months	
DI013	The ACME Laboratories Ltd., Court de la ACME, 1/4, Mirpur Road, Kallayanpur, Dhaka, 1207, Bangladesh	FPP manufacturing site: The ACME Laboratories Ltd., Solid Dosage Unit, Dhulivita, Dhamrai, Dhaka, 1350, Bangladesh API manufacturing site: Dr Paul Lohmann GmbH KG, Haupstrasse 2, Emmerthal, 31860, Germany	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC: 10 x 10's	2-Nov-21	24 months	Do not store above 30°C. Protect from moisture and light.

SRA-approved products

As of June 2022, there are no SRA-approved zinc dispersible tablets/oral solution for use in treatment of diarrhea in children,[1] probably because the disease is much rarer and is treated differently in high-income countries.

When manufacturers claim products are approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

Apart from the WHO-prequalified products listed in Table Z-1 above, zinc sulfate 20 mg dispersible tablet manufacturers approved as suppliers by UNICEF are considered trusted sources. UNICEF selects manufacturers among GMP approved manufacturers via tenders (UNICEF contract awards) to supply products usually over a two- or three-year period. The manufacturer KBI (Germany) is listed by UNICEF as a contract award in 2020 to supply ORS and zinc tablets co-pack.

It is recommended to check for updated information on the UNICEF website at the time of procurement.[2]

Related products

Zinc oral solution may be available at a concentration of 20 mg/5 mL. The recommended zinc dosage is 10–20 mg/day given for 10–14 days to all children with diarrhea. As it is difficult to accurately

[1] Zinc supplements approved and marketed in SRA countries are of different strengths and to be used for the treatment of zinc deficiency

[2] Available at https://www.unicef.org/supply/contract-awards

measure one-half teaspoon of solution, it is recommended that oral solution in the concentration of 10 mg/5 mL be procured for convenient use and avoidance of dosing errors.

STORAGE, STABILITY, AND DEGRADATION

Zinc products have no cold chain storage complications.

Shelf life: 36 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage conditions: Do not store above 30°C. Do not freeze. Protect from moisture and light.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications,[1] such as those of USP and BP, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

In view of the requirements of the WHO guidance document on production of zinc tablets and zinc oral solutions,[2] the following specifications are also recommended:

- Treatment is recommended as 10 or 20 mg as a single dose. Therefore, it is expected that any tablet formulation containing 20 mg elemental zinc per tablet should be scored to facilitate breaking. A subdivision test should be carried out to demonstrate tablets can be divided into equal halves. The uniformity of dose in the tablet halves should be demonstrated.
- Since adherence to the treatment regimen will be affected if the product is not acceptable to infants, young children, and their mothers, zinc preparations should be formulated in such a way as to mask the strong, bitter metallic aftertaste of zinc to enhance acceptability. Evaluation of taste masking and taste acceptability for both tablet and oral solution formulations should be conducted during product development using a standard methodology as described in the WHO guidance document on production of zinc tablets and zinc oral solutions, which is summarized in the Annex.

[1] As of June 2022, there are no monographs of zinc tablets and zinc oral solutions published in the International Pharmacopeia. Updated information should be checked at http://apps.who.int/phint/en/p/about/

[2] World Health Organization. 2007. Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers. Geneva: WHO. Available at https://apps.who.int/iris/rest/bitstreams/51755/retrieve or https://www.who.int/publications/i/item/9241594942?msclkid=a1f20bcccf6a11ecbd0bf5728dfb9227

Table Z-67. US Pharmacopeia Specifications for Zinc Sulfate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Sulfate	A white precipitate is formed.	As per USP monograph of zinc sulfate tablets
b) Zinc	A white precipitate is formed. When an additional 2 mL of sodium hydroxide solution is added, the precipitate dissolves. When 10 mL of ammonium chloride solution is added, the solution remains clear. When 0.1 mL of sodium sulfide solution is added, a white precipitate is formed.	As per USP monograph of zinc sulfate tablets
Assay (zinc sulfate monohydrate)	95.0–105.0%	Titration, USP<541>
Disintegration	Not more than 60 seconds	USP<701>
Uniformity of dosage units	Meet the requirements	USP<905>

Table Z-68. British Pharmacopeia Specifications for Zinc Sulfate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Yields the reactions characteristic of zinc and zinc salts.	Appendix VI
b) Sulfate	Yields the reactions characteristic of sulfates.	Appendix VI
Assay (zinc sulfate monohydrate)	95.0–105.0%	Titration, Appendix VIII D
Disintegration	Not more than 60 seconds*.	Appendix XII A
Uniformity of dosage units	Meet the requirements.	Appendix XII C

** The BP monograph indicates that the tablet should comply with the requirements for the general chapter on 'tablets' and the acceptance criteria is established based on the WHO Q&A: Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution) available at: https://extranet.who.int/pqweb/sites/default/files/documents/50%20Q%26A%20zinc%20sulfate%20tablets_Nov2016_newtempl.pdf*

Table Z-69. US Pharmacopeia Specifications for Zinc Sulfate Oral Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Meets the requirements.	USP<191>
Identification b) Sulfate	Meets the requirements.	USP<191>
pH	2.5–4.5	USP<791>
Specific gravity	1.18–1.24	USP<841>
Assay (zinc sulfate monohydrate)	90.0–110.0%	Titration, USP<541>

Table Z-70. US Pharmacopeia Specifications for Zinc Gluconate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) TLC	The principal spot from the Sample solution corresponds in color, size, and Rf value to that from the Standard solution.	As per USP monograph of zinc gluconate tablets Chromatography ⟨621⟩, Thin-Layer Chromatography.
b) Chemical reaction	A white precipitate is formed after the first addition of sodium hydroxide solution. The precipitate dissolves after the second addition of sodium hydroxide solution. The solution remains clear after addition of ammonium chloride solution, and a white precipitate forms after addition of sodium sulfide solution.	As per USP monograph of zinc gluconate tablets
Assay (zinc sulfate monohydrate)	93.0–107.0%	As per USP monograph of zinc gluconate tablets
Disintegration	Not more than 60 seconds.	USP<701>
Disintegration and dissolution of dietary supplements	Not less than 75% of the labeled amount of zinc gluconate is dissolved.	USP<2040>
Uniformity of dosage units	Meets the requirements.	USP<905>

Table Z-71. US Pharmacopeia Specifications for Zinc Acetate Oral Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Meets the requirements.	USP<191>
b) Acetate	Meets the requirements.	USP<191>
pH	5.7–6.3	USP<791>
Assay (zinc acetate dihydrate)	90.0–110.0%	Titration, USP<541>
Microbial enumeration test	The total aerobic microbial count does not exceed 10^2 cfu/mL. The total molds and yeasts count does not exceed 10^1 cfu/mL.	USP<61>
Tests for specified microorganisms	Absence of *Escherichia coli*	USP<62>

WHO guidance on the study for the scored tablets[3]

When the tablet is functionally scored to facilitate the breaking, a study should be undertaken to ensure the uniformity of dose in the tablet halves. The manufacturer should provide a description of the test method, individual values, mean and relative standard deviation (RSD) of the results.

The content uniformity testing should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (e.g., the splits) would be 10 halves for bisected tablets (one-half of each tablet is retained for the test). The splitting

[3] Refer to World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 to WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46th report. Technical Report Series No. 970. Geneva: WHO.

of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g., manually split by hand). The content uniformity is determined by measuring the content of each of 10 halves using the assay method described in the US or British Pharmacopeia. While in the assay, no fewer than 20 tablets are powdered, and only a portion of this powder is used to make a zinc sulfate solution; in the content uniformity test, each halve is powdered and used separately to make a solution of zinc sulfate. The content of each half is then determined and used for calculating the acceptance value.

The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the routine finished product specifications.

ZINC ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Zinc (as sulfate) 20 mg dispersible tablets is indicated for the treatment of acute and persistent diarrhea in infants and children up to 5 years of age.

Posology, method, and duration of administration

For children below 6 months of age: 10 mg (½ tablet) once daily for 10–14 days

For children 6 months–5 years of age: 20 mg (1 tablet) once daily for 10–14 days

The tablet (or half tablet) should be dispersed completely in 1 teaspoon (5 mL) of clean water or breast milk and the entire amount administered orally to the infant or child.

It is recommended that doses be administered between meals, and a repeat dose given if vomiting occurs within 30 minutes.

For missed doses, the missing dose can be taken as soon as possible, unless there is less than 6 hours remaining until the next dose.

Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Copper deficiency.

Special warnings and precautions for use

Drugs that may inhibit zinc absorption, such as penicillamine, sodium valproate, and ethambutol, should not be co-administered with zinc (as sulfate) 20 mg dispersible tablets, unless the risks of discontinuation of the drug are judged to outweigh the benefit of zinc in treatment of the child's diarrhea.

Accumulation of zinc may occur in cases of renal failure.

Excipients

Zinc (as sulfate) 20 mg dispersible tablets contain aspartame, a source of phenylalanine. This should be considered when prescribing the product to patients with phenylketonuria.

Interaction with other medicinal products and other forms of interaction

Antibiotics

When taken together, zinc may reduce the absorption of tetracyclines (but not doxycycline), and quinolone antibiotics. In addition, zinc may also interfere with the absorption of cephalexin or ceftibuten. An interval of at least 3 hours should be allowed between administration of zinc and any of these medicines.

Medicines that reduce the absorption of zinc such as penicillamine should not be taken together with zinc dispersible tablets. An interval of at least 3 hours should be allowed between administration of zinc and medicines such as penicillamine.

Copper

Zinc may inhibit the absorption of copper.

Calcium salts

The absorption of zinc may be reduced by calcium salts.

Iron

The absorption of zinc may be reduced by oral iron, also the absorption of oral iron may be reduced by zinc.

Trientine

The absorption of zinc may be reduced by trientine, also the absorption of trientine may be reduced by zinc.

Pregnancy and lactation

Pregnancy

The safety of zinc (as sulfate) 20 mg dispersible tablets in pregnancy has not been established.

Lactation

Zinc crosses the placenta and is present in breast milk. The safety of zinc (as sulfate) 20 mg dispersible tablets in lactation has not been established.

Effects on ability to drive and use machines

There is no evidence regarding the effect of zinc on the ability to drive or use machinery, however zinc (as sulfate) 20 mg dispersible tablets is not expected to have any effect on these abilities.

Undesirable effects

In clinical trials in children, administration of zinc (as sulfate) 20 mg dispersible tablets was associated with vomiting or regurgitation. In one study, vomiting attributed to the tablet was reported very commonly (≥ 10%) and regurgitation was reported commonly (≥ 1% to <10%)—in 5.2% in 14% and 5.2% of children, respectively. In most cases, vomiting or regurgitation occurred shortly after administration of the first dose (within 10 minutes) and was not recurrent. Zinc salts may also cause abdominal pain and dyspepsia (frequency unknown).

Zinc may interfere with the absorption of copper, leading to reduced copper levels, and potentially copper deficiency. The risk of copper deficiency may be greater with long-term treatment and/or with higher doses of zinc.

The adverse reactions considered related to zinc sulfate are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100 to 1/10), uncommon (1/1000 to 1/100), rare (1/10 000 to 1/1000), and very rare (< 1/10 000).

- Gastrointestinal disorders
  - Very common: vomiting
  - Common: regurgitation
  - Frequency not known: abdominal pain, dyspepsia, nausea, gastric irritation and gastritis
- Nervous system disorders
  - Frequency not known: headache
- General disorders
  - Frequency not known: irritability, lethargy

Overdose

Symptoms

High doses of zinc cause emesis. In addition, zinc sulfate is corrosive at high doses, and may cause irritation and corrosion of the gastrointestinal tract, including ulceration of the stomach and possible perforation. Overdosage with zinc has also been associated with acute renal tubular necrosis and interstitial nephritis. Prolonged high dose zinc supplementation may result in copper deficiency.

Treatment

In cases of acute zinc overdose, treatment is primarily supportive; however, giving milk, alkali carbonates induced emesis, gastric lavage, or activated charcoal may be useful in cases of substantial ingestions of zinc tablets. Chelating agents such as calcium disodium EDTA may be useful.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform the full prequalification of zinc products. When assessing the complete quality/CMC documentation, assessors should consider the following information on zinc tablets and oral solutions.

API

Any soluble zinc salts (e.g., sulfate, gluconate, acetate, or citrate) may be used for the formulation of the tablets and oral solutions.

As of June 2022, there are two zinc sulfate APIs prequalified by the WHO PQP.

Table Z-72. Manufacturers of WHO-Prequalified Zinc Sulfate API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RETEST PERIOD OR SHELF LIFE	DATE OF PRE-QUALIFICATION
WHOAPI-146	Canton Laboratories Pvt Ltd	Canton Laboratories Pvt Ltd, Survey No. 350 Mujpur Taluka: Padra Vadodara Gujarat 391440, India	Do not store above 30°C.	60 months	12/7/2016
WHOAPI-232	Dr Paul Lohmann GmbH KG	Dr Paul Lohmann GmbH KG, Haupstrasse 2 31860 Emmerthal Germany	Do not store above 30°C; protect from moisture.	36 months	7/3/2014

Three manufacturers of zinc have obtained a certificate of suitability to monographs of the European Pharmacopeia (CEP), confirming its suitable quality for use in medicinal products.

Table Z-73. Manufacturers of Zinc Sulfate API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Zinc sulfate heptahydrate (monograph number 111)	Macco Organiques, SRO CZ 792 01 Bruntál, Czech Republic	R0-CEP 2015-375-Rev 00	5/25/2022	Chemical
Zinc gluconate (monograph number 2164)	Givaudan-Lavirotte FR, 69008 Lyon, France	R1-CEP 2012-221-Rev 00	5/10/2019	Chemical
Zinc acetate dihydrate (monograph number 1482)	Quality Chemicals S.L. Esparreguera Spain	R0-CEP 2018-117 - Rev 00	6/3/2020	Chemical

Other manufacturers of zinc should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

API specifications of zinc should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP) with additional tests/limits for arsenic; as well as for lead, alkalis, and alkaline earths and iron if not included in that monograph. Such additional tests may be based on another pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

Zinc salts (sulfate, gluconate, acetate, citrate) should be kept in a well-closed, non-metallic container.

Zinc gluconate is a hygroscopic material and should be protected from atmospheric moisture.

Excipients

The excipients of zinc sulfate tablets include typical tablet diluent (e.g., microcrystalline cellulose), disintegrant (e.g., colloidal anhydrous silica or crospovidone), and lubricant (e.g., magnesium stearate). Furthermore, the tablets may contain one or more suitable flavors and sweeteners for greater acceptability.

The potential impact of interactions between zinc ions and excipients on absorption is very difficult to predict. The typical tablet diluent, disintegrant, and lubricant excipients are not expected to have a significant impact on absorption due to either minimal reactivity or being present in limited quantities. There is particular concern with respect to the potential impact of sweeteners and flavors on the in vivo absorption of zinc. For this reason, as indicated in the WHO prequalification guidance document Q&A: Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution)[2] and guidance document Advice on the Selection of Excipients for Zinc Tablets and Solutions,[3] manufacturers must provide evidence that sweeteners/flavors present in their zinc products do not negatively impact the absorption of zinc. The principles are applicable for all zinc salts (e.g., sulfate, gluconate, acetate, and citrate).

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46th report. WHO Technical Report Series, No. 970. Geneva: WHO.

[2] World Health Organization/Prequalification Team. 2016. guidance document Q&A: Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution). Available at https://extranet.who.int/pqweb/sites/default/files/documents/50%20Q%26A%20zinc%20sulfate%20tablets_Nov2016_newtempl.pdf

[3] World Health Organization/Prequalification Team. 2016. Guidance Document: Advice on the Selection of Excipients for Zinc Tablets and Solutions. Geneva: WHO/PQT. Available at https://extranet.who.int/pqweb/sites/default/files/documents/53%20Excipients%20zinc_Nov2016_newtempl.pdf

As an aid to the development of zinc formulations, WHO PQP has determined that the following pharmaceutical sweeteners and flavors can be employed as excipients in zinc formulations, without providing additional evidence that the ingredient does not negatively impact the absorption of zinc:

- Aspartame
- Ethyl vanillin (in quantities < 1 mg per 20 mg zinc sulfate tablet)
- Mannitol
- Mono ammonium glycyrrhizinate*
- Saccharin sodium (in quantities < 1 mg per 20 mg zinc sulfate tablet)
- Sorbitol
- Trusil flavors*

It is important that these excipients are employed in the smallest quantities possible to achieve the desired sweetening/flavoring effect. In particular, the identified excipients (*) should be employed in quantities of no more than approximately 2% of the formulation by mass. If it is judged that the above-noted excipients are employed in quantities above the limit for which there is confidence and that their impact will be negligible, additional information on the impact of that quantity of excipient on zinc absorption may be requested for assessment.

It is important to note that the above WHO PQP advice does not indicate that other sweetening/flavoring excipients are not acceptable; it indicates that the use of other sweetening/flavoring excipients must be justified with supporting information on their impact on zinc absorption.

Manufacturing process

Zinc tablets and zinc oral solutions should be manufactured according to recognized principles of GMP, using ingredients that comply with specifications designed to ensure the final products meet the requirements of the compendial monographs.

The uniformity of the batch used in a biowaiver or bioavailability studies should be provided. In addition, a manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In the case where the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three consecutive production scale batches should be submitted.

Notes:

The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.[4, 5]

[4] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[5] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

Packaging

Zinc tablets are usually packed in PVC/PVDC-aluminum foil blister.

Zinc oral solutions are packed in glass or plastic bottles.

Suitability of container should be demonstrated, including:

Safety

- Blister: declarations as to compliance with appropriate food additive regulations (e.g., USFDA or EU regulations).
- Glass/plastic bottles: food grade declaration and tests as per USP<660>/Ph.Eur. 3.2.1 (Glass); USP<661>/Ph.Eur. 3.1.10 (Plastics).

Protection

- Blister: water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671>
- Glass/plastic bottles: plastics WVTR (weight loss) and LT as per USP<671>

Compatibility

- Accelerated and long-term stability data for the packaged finished products.
- A one-time study of extractables (e.g., USP<661> and USP<671>) and leachables (either a study or certification that the materials of construction for packaging components in contact with the product meet the requirements for indirect food additives: e.g., 21 CFR 174–186) is required for oral solutions in plastic bottles.

Oral solutions in multidose containers are required to have a device capable of uniformly dispensing the required range of doses (5–10 mL for 10 mg/5 mL solution). A sample of the device must be provided, along with (1) specifications (with infrared identification of the material); (2) data to demonstrate the uniformity of mass of doses delivered by the measuring device at the lowest intended dose; and (3) the "Instructions on use and handling" should provide clear instructions.

Bioequivalence requirements

As there is currently no comparator product available, a bioequivalence study is not possible. The primary pathway to approval of the safety and efficacy portion of a dossier for most products will be via a biowaiver application. A biowaiver from the requirement to conduct in vivo studies is possible if adequate supporting documentation is provided. The requirements for a biowaiver are described below.

Tablets (dispersible)

The absorption of zinc is sensitive to many factors that affect either gastrointestinal status or the availability of the zinc through interactions such as complexation. For this reason, a waiver from the requirement to provide in vivo study data on the proposed product can be considered under specific circumstances as follows:

- Evidence is provided to demonstrate that the excipients do not negatively impact the absorption of zinc.
- The zinc from the proposed product is proven to be completely in solution after one minute using the solubility test described below.

Effects of excipients on zinc absorption

The potential impact of interactions between zinc ions and excipients on absorption is very difficult to predict. Sweeteners are a significant concern. As is indicated in the WHO guidance document on production of zinc tablets and zinc oral solutions, products may contain one or more suitable flavors and sweeteners to improve acceptability but these substances "should not impair the bioavailability or the therapeutic efficacy or safety of the preparation." For a waiver from in vivo studies to be considered, manufacturers must provide evidence that the sweeteners employed would not negatively affect the absorption of zinc from the formulation. Such evidence can come from either literature or in vitro studies, such as comparative absorption data from cells or infused intestines.

Similar information concerning other excipients may be requested during the product assessment if sufficient information concerning the excipients(s) and their impact on zinc absorption is not available.

Solubility testing

The solubility test should be conducted using tablets from a representative commercial or pilot batch. The percentage of zinc in solution should be assessed under the following conditions:

- One tablet should be immersed in 5.0 mL water at room temperature. The vessel containing the tablet in water should be allowed to sit for one minute without any agitation. After the one minute, the solution should be filtered immediately (e.g., using a syringe filter, and subsequently analyzed for zinc content).
- The quantity of zinc in solution should be calculated as a percentage of the total zinc in the tablet. It is expected that the reported percentage value will be close to the label claim (with tolerance for content and analytical variations).
- A sample size of at least six measurements (n≥ 6) should be conducted.

If it cannot be established that the excipients present in the proposed product formulation do not significantly negatively impact the absorption of zinc, clinical study data are required demonstrating efficacy of the proposed product in the treatment of acute diarrhea or in vivo bioavailability data demonstrating that administration of the proposed product produces adequate plasma levels of zinc within a 72-hour administration period.

Oral solution

The same principles are applicable to oral solution products. For a waiver from the requirement to conduct in vivo studies to be considered, evidence must be provided that the excipients present in the proposed product formulation do not significantly negatively impact the absorption of zinc. If this cannot be established, in vivo study data as described above will be required.

WHO guidance on the evaluation of taste masking[6]

Qualitative evaluation of the taste by a taste panel[7]

Consumer testing is acknowledged as the best method for assessing a product. Consumers are regarded as individuals who are prescreened to be actual users of the product tested with particular interest to product quality. In line with this definition and taking into consideration the sensory

[6] Refer to Annex 7 of World Health Organization. 2007. Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers. Geneva: WHO.

[7] European Medicines Agency. 2005. Reflection Paper: Formulation of Choice for the Paediatric Formulation. EMA/CHMP/PEG/194810/2005. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

differences between adults and children, it is evident that the children as a target population are regarded as the most suitable panel for taste assessment of pediatric formulations.

Recommendations for performing taste trials in children

To design a palatability study in children the following parameters need to be considered as key elements:

- The test should be short to match children's attention span.
- As children are easily distracted, the test must be intrinsically motivating and "fun" to do.
- The procedure must be as easy as possible so that even very young children (e.g., preschoolers) can understand it.
- In order to ensure a reliable assessment, to prevent confusion by the children and taste fatigue, the number of variants to be tested should be limited to a maximum of four.

Palatability studies are not described in any regulatory guidance but must be considered as clinical studies performed by qualified personnel with ethical committee approval and informed consent from parents or guardians and assent from the child as appropriate. There may be ethical difficulties in designing suitable safe studies in which children can easily participate.

Participation and test performance

Generally, children aged 4 years and older are considered able to participate in taste trials. Younger children are very often shy and reluctant. Furthermore, their ability to understand and follow the guidance is sometimes limited; they also lose their interest or may have difficulty concentrating during an entire testing period. The failure rate varies up to 50% depending on the design and duration of the test. In addition, young children are often unable to communicate their feelings and preferences.

To increase children's understanding and motivation it is recommended to start with either high concentrations of the testing agent to be assessed (flavor or sweetener) or with known compounds (e.g., commonly used flavors) followed by the more specific, unusual one (e.g., strawberry or cherry followed by passion fruit). In some cases, to begin the test with high concentrations of a testing agent (e.g., sweetener) would be inappropriate due to the unpleasant sweet taste or the bitter aftertaste. Procedures to remove the previous taste may include repeated rinsing of the mouth, eating of salty crackers, and a sufficiently long interval between sessions.

Sensory evaluation: affective and analytical testing, and ranking

Probably the most critical item in sensory evaluation is defining the objective. The test objective will determine the type and age of subjects and the methodology for design, conduct, and interpretation of the study and its outcome. Considerations include the following:

- Affective testing includes acceptance/preference testing. Typical questions addressed are "which sample do you prefer," "how much do you like it," and "what don't you like."
- Analytical testing requires the use of objective sensory methodologies with the aim of determining the characteristics/properties of the test item, without defining acceptance/preference measures. Analytical testing answers questions such as "which sample is more bitter" or "which sample is different." Analytical methods help define the sensory properties of the medicinal product preparation and differentiate between variants but will not directly predict how much a variant will be liked. It is often used as a technical tool to support development/optimization purposes.

- Ranking is a very straightforward method that can be used for preference or analytical assessment ("please rank samples in order of your personal preference" or "please rank samples in increasing order of bitterness," respectively). The advantage of this method is its simple procedure. However, the study results may be biased due to limited memory and attention of the tester during the entire testing period. This limitation may be more pronounced depending on the age of the subjects participating.

Evaluation principles

In most cases smell, texture, taste and aftertaste, and sometimes also appearance (e.g., if colored) are addressed. Language used in the questionnaire should be simple, intelligible, and plain for all participants independent of their age, social skills, and developmental level. It is recommended to use common, familiar terms relevant to the age of the participants to describe these properties, such as:

- Sweet, salty, sour, and bitter for characterizing the taste
- Thin, thick, viscous, gritty, for describing the texture of the testing item
- Sweet, salty, sour, and bitter but also astringent, numbness, or freshness, for describing the aftertaste

The following two principles for taste evaluation are established in palatability studies with children: verbal judgment and facial hedonic scale.

- Verbal judgment followed by scoring in a scale of, for example, 1–5, with a score of 1 corresponding to very good and a score 5 to very bad, facilitates the statistical evaluation of the data obtained
- By contrast, the facial hedonic scale allows the expression of preferences using a pictorial scale.

Children younger than 5–6 years are not considered able to express differences in taste perception by use of the preferential method. A reliable estimation of differences particularly in this age group (< 5 years) might be achieved using the child's own spontaneous verbal judgments following a control question. The facial hedonic scale cannot be used solely to discriminate between the tastes of tested formulations in the lowest age group. Young children may link the figures with things other than taste (e.g., happy face = I will not stay longer in hospital, sad face = pain or discomfort). Facial expressions and behavior pattern of the subject (making wry faces, shrugging shoulders, vomiting, or spitting the formulation out) may also reflect the acceptance of the tested formulation. To assure reliable outcome of a palatability study with young children, it is suggested to involve parents, guardians, or health providers in the study, asking about any discomfort or other observations in relation to the acceptance of the study medicine. Since older children judge more critically than younger ones, they are able to discriminate between the formulations using both the verbal judgment and hedonic scale.

Independent of the age of the children and the evaluation principle selected, it is suggested to include in the questionnaire concluding questions to the overall taste evaluation of the formulation such as "which formulation was the best" or "which formulation tasted worst." Similar approaches may be followed for the assessment of the flavor used: "which of the tested flavors did you like the most" or "which one did you dislike the most."

WHO guidance on the acceptability study[8]

The acceptability study is considered a clinical trial, and therefore should be performed by qualified personnel, following ethical committee approval, and with the informed consent of parents or guardians. Study conduct must therefore conform to accepted ethical standards (i.e., ICH2 Good Clinical Practices and the Declaration of Helsinki).

The study should be conducted in the community, in children with acute diarrhea. Results from children hospitalized with severe diarrhea will be of limited validity. However, children may be enrolled at clinics, including hospital facilities, where they present for treatment, and this may provide a favorable setting for assessment of the taste acceptability of the tablets or solution, due to the availability of trained personnel, for example.

An essential component of the acceptability study is assessment of adherence to a complete treatment regimen. Consequently, children should be prescribed zinc tablets or solution, 10 or 20 mg per day according to age, for 10–14 days, and a visit is arranged for 2 weeks later, possibly at the home of the child, to assess acceptability of and adherence to the zinc treatment.

The study population should consist of children, aged 3–59 months, with an acute diarrhea episode. Based on statistical considerations,[9] the study should aim to recruit 300 subjects, including 150 children up to the age of 18 months, and 150 children older than 18 months.

Children should be excluded if they are severely dehydrated (e.g., require hospitalization); have taken any other prescription drugs during the preceding 24 hours; have known food or drug allergies to any of the constituents of the test product; or have a medical condition that could interfere with the ability to discriminate taste, for example the common cold, or a sinus or bronchial infection.

Acceptability is assessed based on the caregiver's report of the child's behavior when given the medicine. The caregiver is asked about his or her perception of the taste of the zinc preparation given to the child, compared to other medicines. The possible responses are better, same, or worse than other medicines.

Adherence is assessed by the number of doses of medication taken by each child.

A treatment is generally considered to have good acceptability if 80% of the prescribed treatment is taken by at least 70% of the children.

[8] Refer to Annex 8 of World Health Organization. 2007. Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers. Geneva: WHO.

[9] To identify a ± 7.5% minimal difference in acceptability between children aged over and below 18 months with an anticipated 70% acceptability (p), setting the confidence level at 95% (z = 1.95), the resulting sample size estimate is 140 children per group. To adjust for potential dropouts, it is necessary to add 10 children in each group, for a final target sample of 300 children (150 in each age group).

SUPPLEMENTAL ANNEX: BEST PRACTICES IN SUBNATIONAL PROCUREMENT OF MNCH COMMODITIES IN THE PUBLIC SECTOR

BEST PRACTICES IN SUBNATIONAL PROCUREMENT OF MNCH COMMODITIES IN THE PUBLIC SECTOR

In response to political reform or problems with centrally controlled health product supply, many low- and middle-income countries have decentralized the procurement of health commodities, including those for maternal, newborn, and child health (MNCH), to a province, district, or even facility level. However, if good procurement practices are not in place, such as appropriate standard operating procedures, oversight, and management of conflicts of interest, subnational procurement can compromise product quality, affordability, and ultimately, availability. A 2022 study of subnational procurement of MNCH medicines in ***Nepal***, for example, found widespread use of direct purchasing and weak procurement methods that resulted in a wide range of prices, with lower levels of the health system generally paying substantially higher prices.

These core objectives of good procurement practices should be an integral part of both central and subnational procurement:

- Value for money and optimized use of available resources
- Transparent, impartial, and accountable processes followed with integrity.
- Use of formal, written procedures
- Systems supporting the achievement of good procurement practice and assurance of product and service quality

A Guide to Best Practices in Subnational Procurement of MNCH Commodities in the Public Sector uses case studies and other examples to describe best practices to procure quality-assured, low-cost MNCH medicines and supplies plus three mechanisms to address subnational procurement challenges:

- **Central framework agreements** for frequently procured essential pharmaceuticals and supplies aggregate demand across multiple health facilities, into national or regional contracts, to leverage the buying power of larger volumes. The guide shares three countries' experiences with using framework agreements—***South Africa, New Zealand,*** and ***Liberia***.
- **Prime vendor programs**, where a government contract establishes a private sector pharmaceutical wholesaler/distributor as the primary supplier of medicines and medical supplies for public health facilities. In ***Tanzania's*** public-private partnership, Jazia, health facilities procure priority medicines directly from a prime vendor through a regional contract, which complements regular government supply from the central level.
- **e-procurement systems** provide subnational governments with easy access to framework agreements and prices as well as facilitate transparency and standardization. The guide describes ***Indonesia's*** e-procurement system, which was launched in 2012.

In addition, performance-based financing can bolster efforts to decentralize procurement responsibilities by shifting decision-making to health facilities and pairing it with incentives to improve service quality, including the availability of essential medicines and supplies. Programs in ***Tanzania*** and ***Cameroon*** had some success under this approach.

Decentralized procurement can improve the availability of essential medicines including those used for MNCH; however, if implemented without good procurement practices, the method may compromise quality, affordability, and ultimately availability, which would have a detrimental effect on access and quality of care. Subnational procurement systems, therefore, need measures to guarantee product quality and affordability and a transparent, fair process, although those measures require significant time, financial resources, and political capital, in addition to stakeholder collaboration.