

MODULE III

TECHNICAL INFORMATION FOR  
LIFE-SAVING MNCH PRODUCTS

OXYTOCIN  
MISOPROSTOL  
MAGNESIUM SULFATE  
GENTAMICIN  
7.1% CHLORHEXIDINE DIGLUCONATE  
AMOXICILLIN  
ORAL REHYDRATION  
ZINC



## MODULE III

# TECHNICAL INFORMATION FOR LIFESAVING MNCH PRODUCTS

This module provides useful technical information on the UNCoLSC's life-saving MNCH products to assist the 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 full assessment is necessary. The information provided in this module is based on review of compendial monographs and literature, and on internal expert consultations.

The following UNCoLSC's life-saving MNCH products are included in this module .

 <b>Maternal health</b>	 <b>Newborn</b>	 <b>Child health</b>
<b>Oxytocin</b> Injection 10 IU in 1-mL	<b>Gentamicin</b> Injection 10 mg/mL in 2 mL vial 40 mg/mL in 2 mL vial	<b>Amoxicillin</b> Dispersible tablets, 250 mg
<b>Misoprostol</b> Tablets, 200 micrograms	<b>7.1% chlorhexidine digluconate</b> Solution or gel	<b>Oral rehydration</b> Solution
<b>Magnesium sulfate</b> Injection 500 mg/mL in 2-mL 10-mL ampoule		<b>Zinc</b> Sulfate, gluconate, acetate, and citrate; dispersible tablets 10 mg, 20 mg; oral solution 10 mg per unit dosage



# 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 an uterotonic medicine to increase muscle contractions in the uterus that compress the blood vessels. Oxytocin is recommended by WHO as the first-line medicine for the prevention and treatment of postpartum hemorrhage. 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, ergotamine and ergometrine, have some drawbacks. Misoprostol is the second-line medicine, recommended by the WHO for the prevention and treatment of PPH only when oxytocin use is not feasible. It is recommended for use in women giving birth outside of a health facility (e.g., home deliveries), as it is administered by pill rather than by injection. Ergotamine and ergometrine have more side effects, should only be given after the birth of the placenta, must be kept in the cold chain, and are contraindicated for many conditions, including 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.

## 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.

## 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 Annex A2 item 4.

### **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.

## Oxytocin

<b>Name of the Medicinal Product</b>	Oxytocin injection
<b>Chemical Name</b>	<p>Oxytocin (L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide)</p> <p>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.</p>
<b>Chemical Structure</b>	$\text{C}_{43}\text{H}_{66}\text{N}_{12}\text{O}_{12}\text{S}_2$ <p>H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH<sub>2</sub></p>
<b>Pharmaceutical Form</b>	<p>Sterile solution for injection</p> <p>A clear, colourless solution</p>
<b>Qualitative and Quantitative Composition</b>	<p>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.</p> <p>List of possible excipients<sup>1</sup>:</p> <ul style="list-style-type: none"><li>- Acetic acid</li><li>- Chlorobutanol</li><li>- Ethanol</li><li>- Sodium acetate trihydrate</li><li>- Water for injection</li></ul>
<b>Packaging and Presentation</b>	<p>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.</p>

<sup>1</sup> Based on the formulation of an innovator product, Syntocinon®.

## 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 February 2018, two 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/prequal/content/prequalified-lists/medicines>.

Table O-1. List of WHO Prequalified Oxytocin Injection

WHO REF. NUMBER	RH050	RH053(a)
MARKETING AUTHORIZATION HOLDER	PT Sanbe Farma, Jl. Taman Sari no. 10, Bandung, 40116, Indonesia	Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia
MANUFACTURING SITE	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	FPP manuf. site: HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia
	API manuf. site: Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia	API manuf. site: Grindeks JSC, 53 Krustpils Street, Riga, 1057, Latvia
DOSAGE FORM AND STRENGTH	Solution for injection 10 IU/mL	Solution for injection 10 IU/mL
PACKAGING AND PRESENTATION	Ampoule; Type I glass 1 mL x 10's	Ampoule; Type I glass 1 mL x 5's 1 mL x 10's
DATE OF PRE-QUALIFICATION	June 30, 2017	April 16, 2015
SHELF LIFE	18 months	48 months
STORAGE CONDITION	Store in refrigerator (2–8°C), do not freeze, protect from light.	Store in refrigerator (2–8°C), protect from light.

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

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	Novartis Pharmaceuticals UK Ltd, UK	PL 00101/0960	Clear glass 1-mL ampoule	5 years	Store in refrigerator (2–8°C). May be stored up to 30°C for 3 months, but must then be discarded.
Oxytocin 10 IU/mL solution for infusion	UK MHRA	Peckforton Pharmaceuticals Ltd, UK	PL 15760/0036	Transparent Ph. Eur. type I glass 1-mL ampoule	4 years	Store in refrigerator (2–8°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 in refrigerator (2–8°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 in refrigerator (2–8°C). May be stored up to 30°C for 3 months, but must then be discarded.
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 be discarded.
Oxytocin Medipha Sante 10 IU/mL concentrate for solution for infusion	UK MHRA	Medipha Sante, France	PL 34760/0006	Clear glass 1-mL ampoule	3 years	Store in refrigerator (2–8°C).
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.
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.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
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
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
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® 10 IU/mL injection ampoule	TGA Australia	Novartis Pharmaceuticals Australia Pty Ltd, Australia	AUST R 13383	Clear glass 1-mL ampoule	Not specified	Store in refrigerator (2–8° C). Do not permit to freeze.
Oxytocin Sandoz® 10 IU/mL injection ampoule	TGA Australia	Sandoz Pty Ltd, Australia	AUST R 162499	Clear glass 1-mL ampoule	Not specified	Store in refrigerator (2–8° C). Do not freeze.
Oxytocin Aspen® 10 IU/mL injection ampoule	TGA Australia	Aspen Pharmcare Australia Pty Ltd, Australia	AUST R 164131	Clear glass 1-mL ampoule	Not specified	Store in refrigerator (2–8° C). Do not freeze. 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.

\* 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 or equivalent, patient information leaflet or equivalent, 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:

- 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](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 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 pharmacopoeial specifications, such as those of the International Pharmacopoeia (IP), US Pharmacopoeia (USP), and British Pharmacopoeia (BP), depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopoeias are similar, except the pH, related substances, and/or bacterial endotoxin limits.

Table O-3. International Pharmacopoeia 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.	I.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.	I.14.4 HPLC
pH	pH of the injection, 3.0 – 5.0	I.13 pH value
Assay	90.0–110.0%	I.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%).	I.14.4 HPLC

Test	Acceptance Criteria	Analytical Method
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
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table O-4. US Pharmacopoeia 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 <i>assay preparation</i> corresponds to that in the chromatogram of the <i>standard preparation</i> as obtained in the <i>assay</i> .	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 ( $\pm 0.1$ 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>

Test	Acceptance Criteria	Analytical Method
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<I>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table O-5. British Pharmacopoeia 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
Bacterial endotoxins	Comply	As in Ph.Eur. 2.6.14
Sterility	Sterile	As in Ph.Eur. 2.6.1
Extractable volume	Comply	As in Ph.Eur. 2.9.17
Particulate matter	Comply	As in Ph.Eur. 2.9.19



# PART I: 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

*Induction or stimulation of labor:* Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor.

Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.

An intravenous infusion of a non-oxytocin containing solution should be started. Physiologic electrolyte solutions should be used except under unusual circumstances.

To prepare the usual solution for intravenous infusion, one mL (10 units) of oxytocin is combined aseptically with 1,000 mL of a non-hydrating diluent.

The combined solution, rotated in the infusion bottle to ensure thorough mixing, contains 10 milliunits (mU) of oxytocin per mL. Add the container with dilute oxytocic solution to the system through the use of a constant infusion pump or other such device to control accurately the rate of infusion.

The initial dose should be no more than 1–2 mU/minute. The dose may be gradually increased in increments of no more than 1–2 mU/minute, until a contraction pattern has been established which is similar to normal labor.

The fetal heart rate, resting uterine tone, and the frequency, duration, and force of contractions should be monitored.

The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and fetus must be evaluated by the responsible physician.

*Incomplete, inevitable, or missed abortion:* Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20–40 drops/minute.

*Cesarean section:* 5 IU by intravenous infusion after delivery of the fetus.

*Prevention of postpartum uterine hemorrhage:* 10 IU by intramuscular injection or intravenous infusion after delivery of the baby, after checking that there is no second (or third) child in utero. In women given oxytocin for induction or stimulation of labor, the infusion should be continued at an increased rate during the third stage of labor and for the next few hours thereafter.

*Treatment of postpartum uterine hemorrhage:* 10–40 units of oxytocin may be added to 1,000 mL of a non-hydrating diluent and given by intravenous infusion run at a 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

Oxytocin must only be administered as an intramuscular injection or intravenous infusion and never by intravenous bolus injection as it may cause an acute 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.

### 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).

This guidance should be followed when oxytocin is given for induction and enhancement of labor:

- Fetal distress and fetal death: Administration of oxytocin at excessive doses results 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.
- Borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy induced hypertension or cardiac disease, and in patients above 35 years of age or patients with a history of lower-uterine-segment cesarean section: Particular caution is required in these conditions.
- Disseminated intravascular coagulation: In rare circumstances, the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (DIC). The 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.

### Intrauterine death

In the case of fetal death in utero, and/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 possesses slight antidiuretic activity, its prolonged intravenous administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum hemorrhage, may cause water intoxication associated with hyponatremia. 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. 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 dextrose); 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; 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.

## **Interaction with other medicinal products and other forms of interaction**

### **Prostaglandins and their analogues**

Prostaglandins and their analogues facilitate contraction of the myometrium; therefore oxytocin can potentiate the uterine action of prostaglandins and analogues and vice versa (see “[Contraindications](#)” section above).

### **Medicines prolonging the QT interval**

Oxytocin should be considered as potentially arrhythmogenic, particularly in patients with other risk factors for torsades de pointes, such as medicines which prolong the QT interval or in patients with history of long QT syndrome (see “[Special warnings and precautions for use](#)” section above).

### **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/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.

## **Pregnancy and lactation**

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.

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.

### Effects on ability to drive and use machines

Oxytocin can induce labor; therefore caution should be exercised when driving or operating machines. 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.

Rapid intravenous bolus injection of oxytocin at doses amounting to several IUs may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia (see "Special warnings and precautions for use" section above). These rapid hemodynamic changes may result in myocardial ischemia, particularly in patients with preexisting cardiovascular disease. Rapid intravenous bolus injection of oxytocin at doses amounting to several IUs may also lead to QTc prolongation.

In rare circumstances the pharmacological induction of labor using uterotonic agents, including oxytocin, increases the risk of postpartum disseminated intravascular coagulation (see "Special warnings and precautions for use" section above).

### Water intoxication

Water intoxication associated with maternal and neonatal hyponatremia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see "Special warnings and precautions for use" section above). The combined antidiuretic effect of oxytocin and the intravenous fluid administration may cause fluid overload leading to a hemodynamic form of acute pulmonary oedema without hyponatremia (see "Special warnings and precautions for use" section above).

Symptoms of water intoxication include:

- Headache, anorexia (loss of appetite), nausea, vomiting, and abdominal pain
- Lethargy, drowsiness, unconsciousness, and grand-mal type seizures
- Low blood electrolyte concentration

Undesirable effects in the tables below are ranked under heading of frequency, the most frequent first, using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); 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. Adverse drug reactions are listed according to system organ classes in the Medical Dictionary for Regulatory Activities (MedDRA). Within each system organ class, ADRs are presented in order of decreasing seriousness.

## Adverse Drug Reactions in Mother

SYSTEM ORGAN CLASS	ADVERSE DRUG 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
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
Skin and subcutaneous tissue disorders	Frequency not known: angioedema

## Adverse Drug Reactions in Fetus/Neonate

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

## Overdose

The fatal dose of oxytocin has not been established. Oxytocin is subject to inactivation 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 February 2018, there is no oxytocin API prequalified by the WHO PQP.

There are five 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 product.

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 00	10/16/2015	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 01	1/10/2014	Chemistry
Oxytocin (monograph number 780)	Shenzhen Jymed Technology Co., Ltd. Cn 518 057 Shenzhen, China	R0-CEP 2015-376-Rev 00	11/27/2017	Chemistry

Other manufacturers of oxytocin API should provide evidences for GMP compliance and API quality documentation as per the WHO guideline.<sup>1</sup>

The specifications of oxytocin API should be in line with a pharmacopoeial 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.<sup>2</sup> There are no special concerns on the excipients.

### 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.<sup>3</sup> that oxytocin is most stable between pH 3 and 5. Hawe et al.<sup>4</sup> also reported that the degradation 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, and

<sup>1</sup> 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.

<sup>2</sup> Based on the formulation of an innovator product, Syntocinon®.

<sup>3</sup> Nachtmann, F., K. Krummen, F. Maxl, and E. Reimer. 1981. “Oxytocin. Analytical profiles of drug substances.” *Analytical Profiles of Drug Substances* 10: 563–600.

<sup>4</sup> 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.

packing operations. Thus, should trace contamination occur during the manufacturing process, the added preservative may render the product sterile.

Where chlorobutanol is included in the formulation as an antimicrobial preservative, 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.

## 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.

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 bulk solution is packed and stored. Suggested conditions for production are temperature 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.

## Packaging

Neutral type I glass ampoule or vial should be used.

Suitability of 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 stopper 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), Pitocin® (oxytocin 10 IU/mL injection, PAR Sterile Products LLC, USA), and oxytocin 10 IU/mL injection (Eurohealth International SARL or Fresenius Kabi LLC, USA). The composition of the proposed product should be the same as the comparator product.



# 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 preferred first-line medicine for the prevention and treatment of PPH, the major 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 to be stored in the cold chain 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.

## 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 product from the manufacturer before ordering as the use of inappropriate excipients or inadequately controlled environmental conditions can also 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. 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.

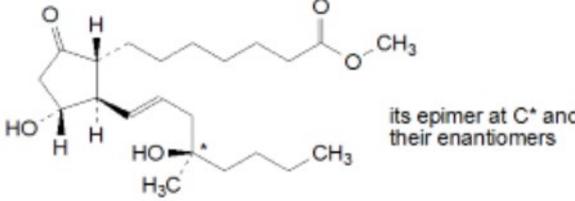
Additional information about the packaging and labeling can be found in the Annex.

### **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.

## Misoprostol

<b>Name of the Medicinal Product</b>	Misoprostol
<b>Chemical Name</b>	(±) methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate
<b>Chemical Structure</b>	<p>C<sub>22</sub>H<sub>38</sub>O<sub>5</sub></p>  <p>The chemical structure shows a prostanoic acid derivative. It features a cyclopentane ring with a carboxylate group at C1 (methyl ester), a ketone at C9, and a double bond at C13. A methyl group is attached to C16, and a hydroxyl group is attached to C16. The structure is labeled as its epimer at C* and their enantiomers.</p>
<b>Pharmaceutical Form</b>	For use in the prevention and treatment of PPH, misoprostol is available in an oral tablet form, which can be administered orally or sublingually.
<b>Qualitative and Quantitative Composition</b>	<p>Each tablet contains 200 micrograms (mcg) of misoprostol.</p> <p>List of excipients<sup>1</sup>:</p> <ul style="list-style-type: none"><li>– Microcrystalline cellulose</li><li>– Hydrogenated castor oil</li><li>– Sodium starch glycolate</li><li>– Hypromellose</li></ul>
<b>Packaging and Presentation</b>	Typically, cold-form double-aluminum blister (Alu/Alu) is used for primary packaging. Secondary packaging is normally suitable cardboard to protect from damage.

<sup>1</sup> Based on the formulation of an innovator product, Cytotec<sup>®</sup>.

## 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

As of February 2018, there are three misoprostol 200 mcg tablets 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/prequal/content/prequalified-lists/medicines>.

Table M-1. WHO-Prequalified Misoprostol 200 mcg Tablets

WHO REF.	MARKETING AUTHORIZATION	MANUFACTURING SITE	DOSAGE FORM AND	PACKAGING AND	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 to L-147-I, S-103 to S-105, S-107 to S-112 and M-61 to M-63, 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, Ropar, 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

Table M-2. 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;	3 years	Do not store above 30°C. Store in the original package to protect from moisture.
				cold-formed aluminum blister pack		
Cytotec*	US FDA	GD Searle LLC, Division of Pfizer Inc	NDA #019268	Oral tablet;	Not specified	Store at or below 25°C, in a dry area.
				bottle		
Misoprostol *	US FDA	Ivax Sub Teva Pharms	ANDA #076095	Oral tablet;	Not specified	Store at 20°–25°C in a dry area. [See USP controlled room temperature.]
				bottle		
Misoprostol *	US FDA	Novel Lab Inc.	ANDA #091667	Oral tablet;	Not specified	Store at 20–25°C. [See USP controlled room temperature.] Store in a dry area.
				bottle		

\* 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.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Cytotec 200 mcg, comprimé sécable*	ANSM, France	Pfizer Holding France	34009 328 785 8 1, 34009 328 786 4 2	Oral tablet; bottle (amber glass), blister pack (PE/PV/C/)	3 years	Not specified
GyMiso 200 mcg, comprimé**	ANSM, France	Linepharma, France	34009 362 499 4 3	Oral tablet; blister pack (paper/PE/)	2 years	Store at a temperature not exceeding 25°C
Cytotec tablets (misoprostol 200 mcg)*	Swissmedic	Pfizer PFE Switzerland, GmbH	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	Proqualix Pty Ltd (in administration)	AUST R 46849	Oral tablet; bottle	Not specified	Not specified
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 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](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 misoprostol that exist in the market include the following products.

<b>Vaginal tablet 25 mcg</b>	Included in the WHO EML, only for use for induction of labor where appropriate facilities are available
<b>Misoprostol oral tablet 100 mcg</b>	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
<b>Misoprostol oral tablet 400 mcg (e.g., Topogyne<sup>®</sup>, Misoone<sup>®</sup>)</b>	Indicated for medical termination of developing intrauterine pregnancy, in sequential use with mifepristone
<b>Misoprostol vaginal 200 mcg vaginal delivery system (e.g., Mysodelle<sup>®</sup>, Misodel<sup>®</sup>)</b>	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

<b>Combination pack of mifepristone and misoprostol (e.g., Medabon®)</b>	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 600 mcg orally for the prevention of PPH, and sublingual misoprostol at 800 mcg for controlling PPH when oxytocin is unavailable.

## 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<sup>2</sup> 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.

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

<sup>2</sup> World Health Organization. 2016. "Quality of Misoprostol Products." In: *WHO Drug Information*. Vol. 30, No. 1. Geneva: WHO. Available at [http://www.who.int/medicines/publications/druginformation/WHO\\_DI\\_30-1\\_Quality.pdf](http://www.who.int/medicines/publications/druginformation/WHO_DI_30-1_Quality.pdf)

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 the table in this module's Sections 2.1 and 2.2, respectively.

## PRODUCT SPECIFICATIONS



The product must meet the International Pharmacopoeia specifications,<sup>3</sup> or the equivalent thereof.

### International Pharmacopoeia

Table M-3. International Pharmacopoeia Specifications for Misoprostol

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): <ul style="list-style-type: none"> <li>– 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%).</li> <li>– 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%).</li> <li>– 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%).</li> </ul>	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 $\pm 15\%$ of the average amount of the active ingredient. However, if one individual unit deviates by more than $\pm 15\%$ but is within $\pm 25\%$ of the average amount of the active ingredient,	5.1 Uniformity of content for single-dose preparations

<sup>3</sup> As of February 2018, there are no monographs of misoprostol tablets published in the US or British Pharmacopoeia; please check for updated information.

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	<p>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 no more than one out of 30 units deviates by more than <math>\pm 15\%</math> of the average amount. None deviates by more than <math>\pm 25\%</math> of the average amount.</p>	
<p>* 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)-11<math>\alpha</math>,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.”</p>		



## PART I: 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

Posology, Method and Duration of Administration for Misoprostol

INDICATION	DOSAGE	NOTES
PPH prevention	600 mcg orally single dose	<ul style="list-style-type: none"> <li>– Included in the WHO EML.</li> <li>– Exclude second twin before administration.</li> </ul>
PPH treatment	800 mcg sublingually single-dose	
Incomplete abortion (first trimester)	600 mcg orally single-dose or 400 mcg sublingually single-dose	<ul style="list-style-type: none"> <li>– Included in the WHO EML.</li> <li>– Leave to work for 1–2 weeks (unless there is heavy bleeding or infection).</li> </ul>
Missed abortion (first trimester)	800 mcg vaginally 3-hourly (max x2) or 600 mcg sublingual 3-hourly (max x2)	<ul style="list-style-type: none"> <li>– Give 2 doses and leave to work for 1–2 weeks (unless there is heavy bleeding or infection).</li> </ul>
Induced abortion (first trimester)	800 mcg vaginally 3-hourly (max x3 within 12 hours) or 800 mcg sublingually 3-hourly (max x3 within 12 hours)	<ul style="list-style-type: none"> <li>– Ideally used 48 hours after mifepristone 200 mg.</li> </ul>
Induced abortion (second trimester)	400 mcg vaginally 3-hourly (max x5) or 400 mcg sublingually 3-hourly (max x5)	<ul style="list-style-type: none"> <li>– Most effective when used 48 hours after mifepristone 200 mg.</li> </ul>

INDICATION	DOSAGE	NOTES
Intrauterine fetal death (second trimester)	13–17 weeks: 200 mcg vaginally 6-hourly (max x4) 18–26 weeks: 100 mcg vaginally 6-hourly (max x4) 27–43 weeks: 25-50 mcg 4-hourly	– Halve dose in women with previous cesarean section.
Intrauterine fetal death (third trimester)	25 mcg vaginally 6-hourly or 25 mcg orally 2-hourly	– Reduce doses in women with previous cesarean section.
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 vaginally 3 hours before procedure or 400 mcg sublingually 2–3 hours before procedure	– Use for insertion of intrauterine device, surgical termination of pregnancy, dilatation and curettage, and hysteroscopy.

## 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.

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

Adverse Reactions from Misoprostol

MedDRA 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 $\geq 40^{\circ}\text{C}$ .	Chills	Fatigue	

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

When used for abortion the following adverse events were reported in addition:

- Uterine cramping, prolonged menstrual-like bleeding, on average for 9 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 experience 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 particular 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 February 2018, only one manufacturer of misoprostol dispersion (1:100 in HPMC) has been prequalified by the WHO PQP.

Manufacturer of WHO-Prequalified Misoprostol API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RETEST 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 (2–8°C), protect from moisture and light.	60 months	4/22/2016

Two manufacturers of misoprostol API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

## Manufacturers of Misoprostol API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Misoprostol (monograph number 1731)	Chinoin Pharmaceutical and Chemical Works Private Co. Ltd, HU 1045 Budapest, Hungary	R0-CEP 2011-333-Rev 01	4/9/2014	Chemistry
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.<sup>1</sup>

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

## Excipients

Excipients must conform to pharmacopeia monographs. The recommendations for the key excipients selection 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<sup>®</sup> microcrystalline cellulose (FMC biopolymer) and their water content are shown below. Other manufacturers of microcrystalline cellulose make products with similar specifications.

#### Grades of Avicel<sup>®</sup> Microcrystalline Cellulose and Their Water Contents

PRODUCT GRADES	NOMINAL PARTICLE SIZE, $\mu\text{M}$	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

<sup>1</sup> 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.*

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

1. 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 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.
2. Grade required for most efficient blending and tablet pressing
  - Selection of a grade which 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 Pharmacopoeias differentiate the properties of sodium starch glycolate types A, B and C as summarized below.

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 the 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 1 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.

### **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 1-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<sup>2</sup>/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.

Comparative Moisture Barrier Properties of Blister Packaging Materials

Typical WVTR G/M <sup>2</sup> /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<sup>®</sup> (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 (C<sub>max</sub>) of at least 200 pg/mL (normalized for a 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 in order to accept the product for the indication of “induction of labor” due to the required administration of fractional doses.

# 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 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 sole first-line treatment of pre-eclampsia and eclampsia that should be procured over other anticonvulsants and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

## 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 pharmacopoeial specifications, such as those of the International Pharmacopoeia, US Pharmacopoeia, and British Pharmacopoeia, 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 are 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 oxytocin injection packaging and labeling can be found at the

### **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.

## Magnesium Sulfate

<b>Name of the Medicinal Product</b>	Magnesium sulfate injection
<b>Chemical Name</b>	Magnesium sulfate (1:1) heptahydrate
<b>Chemical Structure</b>	MgSO <sub>4</sub> , 7H <sub>2</sub> O
<b>Pharmaceutical Form</b>	Sterile solution for injection A clear, colorless solution
<b>Qualitative and Quantitative Composition</b>	<p>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<sup>2+</sup>) per mL.</p> <p>1 ampoule (2 mL) contains 1,000 mg of magnesium sulfate heptahydrate.</p> <p>1 ampoule (10 mL) contains 5,000 mg of magnesium sulfate heptahydrate.</p> <p>List of excipients:</p> <ul style="list-style-type: none"><li>– Water for injections</li><li>– Sulfuric acid and/or sodium hydroxide, for pH adjustment</li></ul>
<b>Packaging and Presentation</b>	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 February 2018, there are five 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/prequal/content/prequalified-lists/medicines>.

Table MS-I. 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	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	2 years	Do not store above 30°C.
RH063	AS Kalceks, Krustpils iela 53, Rīga, LV-1057, Latvia	FPP manufacturing site: HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia  API manufacturing site: K+S KALI GmbH, Werk Werra, Standort Hattorf, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany	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	3 years	Do not store above 30°C.
RH064	AS Kalceks, Krustpils iela 53, Rīga, LV-1057, Latvia	FPP manufacturing site: HBM Pharma sro, Sklabinska 30, Martin, 036 80, Slovakia  API manufacturing site: K+S KALI GmbH, Werk Werra, Standort Hattorf, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany	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	3 years	Do not store above 30°C.

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

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE, FORM, AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH073(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	FPP manufacturing site: Macarthy's 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	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, Romford, Essex, RM3 8UG, United Kingdom	FPP manufacturing site: Macarthy's 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	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.

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

## Magnesium Sulfate

Table MS-2. 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	Store at 2°–25°C.
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).

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 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](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 magnesium sulfate injection on the market include the following products.

<b>Magnesium sulfate 10% w/v</b>	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
<b>Magnesium sulfate 20% w/v</b>	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: 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.

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 pharmacopoeial specifications, such as those of the International Pharmacopoeia, 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 three pharmacopoeias are the same, except for the assay and bacterial endotoxin limits.

Table MS-3. International Pharmacopoeia 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
Identification 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

## Magnesium Sulfate

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Extractable volume	Comply	5.6 Extractable volume for parenteral preparations
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table MS-4. US Pharmacopoeia 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>
Identification 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>
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table MS-5. British Pharmacopoeia 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
Identification 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: 5.5–7.0	Appendix V L
Assay	95.0–105.0%	Titration, BP monograph
Bacterial endotoxins	Comply	Ph.Eur. 2.6.14

## Magnesium Sulfate

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Sterility	Sterile	Ph.Eur. 2.6.1
Extractable volume	Comply	Ph.Eur. 2.9.17
Particulate matter	Comply	Ph.Eur. 2.9.19



# PART I: CLINICAL PARTICULARS

## Therapeutic indications

Pre-eclampsia, eclampsia

## Posology, method, and duration of administration

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  $\leq 20\%$  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 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.

*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.

## Contraindications

Marked bradycardia (slow heartbeat), myasthenia gravis (muscle weakness) and atrioventricular block (disruption of the heart's impulse conduction system) or other cardiac conduction disturbances and diathesis for infection, stones (calcium, magnesium ammonium phosphate stones), severe renal dysfunction, anuria, dehydration

Magnesium sulfate injection should not be co-administered with barbiturates, narcotics or hypnotics, due to the risk of respiratory depression.

## Special warnings and precautions for use

To be used only with special caution in patients with mild to moderately pronounced renal insufficiency.

See also "Overdose" section below.

## Interaction with other medicinal products and other forms of interaction

The effect of magnesium is reduced (antagonism) with concomitant IV administration of calcium salts. Muscle relaxants of the curare type potentiate the effect of magnesium on the motor end plate. Diuretics, aminoglycoside antibiotics (such as gentamicin, tobramycin, amphotericin B), immunosuppressants (such as cyclosporin A) and cytostatics (such as cisplatin), and digitalis glycosides cause increased excretion of magnesium via the kidneys. Interaction with nifedipine should also be taken into consideration, as it can lead to severe hypotension and neuromuscular blockade.

For more details, see also, "Contraindications" section above.

## Pregnancy and lactation

There is no evidence of a risk of malformation. However, documented experience in humans is limited with regard to use during early pregnancy. Therefore, magnesium sulfate injection should only be used during early pregnancy after a careful benefit/risk assessment.

If magnesium is administered shortly before childbirth, the newborn infant should be monitored during the first 24–48 hours of life for signs of toxicity (neurological depression with respiratory depression, muscle weakness, loss of reflexes).

## Effects on ability to drive and use machines

Magnesium sulfate injection has no influence on the ability to drive or use machines.

## Undesirable effects

The following categories are used for stating the frequency of undesirable effects:

- Very common ( $\geq 1/10$ )
- Common ( $\geq 1/100$  to  $< 1/10$ )
- Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )
- Very rare ( $< 1/10,000$ )
- Not known (cannot be estimated from the available data)

Very common: flushing

Common: nausea or vomiting, muscle weakness, absent or reduced tendon reflexes, respiratory depression, reactions at the injection site (pain, burning, swelling, inflammation)

Uncommon: thirst, headache; hypotension, heart palpitations, tachycardia; dizziness, drowsiness or confusion, itching or tingling

In addition, the following may occur: skin rash, hyperkalemia, prolonged bleeding time as well as visual disturbances.

## Overdose

### Symptoms of intoxication

Magnesium intoxication is unlikely when renal function is intact and at the dosage stated. If magnesium intoxication should nevertheless occur, the following symptoms can be observed:

Symptoms of Magnesium Intoxication

MG PLASMA CONCENTRATION IN MMOL/L	POSSIBLE SYMPTOMS, POSSIBLE UNDESIRABLE EFFECTS
> 1.5	Decrease in blood pressure, retching, vomiting
> 2.5	CNS depression
> 3.5	Hyporeflexia, ECG changes
> 5.0	Incipient respiratory depression
> 5.5	Coma
> 7.0	Cardiac arrest, respiratory paralysis

### **Treatment of intoxication**

Reduction of the dose or discontinuation of the medication leads to rapid regression of the undesirable effects.

As an immediate measure (antidote), a slow intravenous calcium injection (10–20 mL of a 10% calcium gluconate solution) can be used.

See also “[Pregnancy and lactation](#)” section above.

With high-dose magnesium sulfate therapy, the following must be checked:

- Monitoring of cardiovascular function
- Patellar tendon reflexes (knee-tendon reflexes); these must be maintained. Dose reduction if they are no longer responsive.
- Respiratory rate should be no less than 16 breaths/minute.
- Urine output should be 25 mL per hour or 100 mL per 4 hours. If it is any lower, there is a risk of hypermagnesemia (excessively high magnesium concentrations in the blood).
- As an antidote, 10% calcium gluconate ampoules must be readily available.
- If the antidote is not sufficient in life-threatening conditions, intensive care measures must be taken.

To be used only with special caution in patients with mild to moderately pronounced renal insufficiency.

## 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 particular information on magnesium sulfate injection.

### API

As of February 2018, no magnesium sulfate API is prequalified by the WHO PQP.

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

Manufacturer 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

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 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.

The specifications of magnesium sulfate API should be in line with a pharmacopoeial 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 pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

### Excipients

The excipients of magnesium sulfate injection include water for injection and sulfuric 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  $F_0$  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.

## Packaging

Neutral type I glass ampoule should be used.

Suitability of 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

## Magnesium Sulfate Annex

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.



# GENTAMICIN

INJECTION, 10 MG/ML IN 2 ML VIAL  
AND 40 MG/ML IN 2 ML VIAL

## GENERAL PRODUCT INFORMATION

Gentamicin injection is the first-line drug recommended by WHO for the treatment of community acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children. 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 as.



## 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 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 neonate<sup>1</sup>.

<sup>1</sup> 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](http://www.path.org/publications/files/PATH_dt_cust_syringe_br.pdf)

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 from manufacturers there is satisfactory stability data to support shelf life and storage conditions.

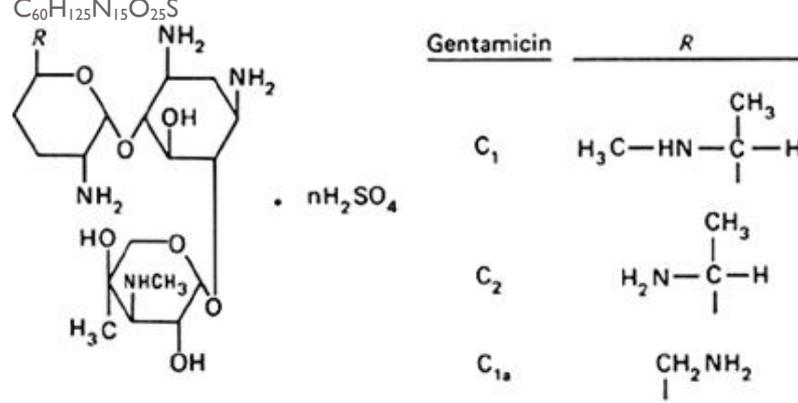
Gentamicin injection does not need to be maintained in the cold chain, but should be stored below 25°C.

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 misoprostol 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.

<b>Name of the Medicinal Product</b>	Gentamicin injection
<b>Chemical Name</b>	Gentamicin sulfate Gentamicin sulfate is the sulfate salt of gentamicin fractions C <sub>1</sub> , C <sub>2</sub> , and C <sub>1a</sub> produced by the growth of <i>Micromonospora purpurea</i> .
<b>Chemical Structure</b>	<p><math>C_{60}H_{125}N_{15}O_{25}S</math></p>  <p><b>Gentamicin</b>      <b>R</b></p> <p>C<sub>1</sub>      H<sub>3</sub>C—HN—C(CH<sub>3</sub>)—H</p> <p>C<sub>2</sub>      H<sub>2</sub>N—C(CH<sub>3</sub>)—H</p> <p>C<sub>1a</sub>      CH<sub>2</sub>NH<sub>2</sub></p>
<b>Pharmaceutical Form</b>	Sterile solution for injection A clear, colorless solution
<b>Qualitative and Quantitative Composition</b>	<p>Gentamicin injection is a sterile solution of gentamicin sulfate in water for injection.</p> <ul style="list-style-type: none"> <li>– Gentamicin injection 10 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 20 mg gentamicin base.</li> <li>– Gentamicin injection 40 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 80 mg gentamicin base.</li> </ul> <p>List of excipients<sup>2</sup>:</p> <ul style="list-style-type: none"> <li>– Sodium chloride</li> <li>– Water for injection</li> <li>– Sulfuric acid and/or sodium hydroxide, for pH adjustment</li> </ul> <p>Some formulations may contain the following excipients:</p> <ul style="list-style-type: none"> <li>– Methylparaben (preservative)</li> <li>– Propylparaben (preservative)</li> <li>– Sodium metabisulfite (antioxidant)</li> <li>– Edetate disodium (chelating agent)</li> </ul>
<b>Packaging and Presentation</b>	The WHO EMLc includes two presentations: 10 mg/mL and 40 mg/mL in 2-mL vial presentation for gentamicin injection. However, some manufacturers sell it packaged in glass ampoules.

<sup>2</sup> Based on the formulation of an innovator product, Cidomycin®.

## 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.

### SRA-approved products

Table G-1. 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.]
Gentamicin sulfate EQ 10 mg base/mL	US FDA	Hospira, USA	ANDA #062612	Single-dose 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, One Onslow Street, Guildford, Surrey, GU1 4YS, UK	PL 04425/0672	Colourless glass ampoules (type I) or colourless 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, Ash Road North Wrexham LL13 9UF, 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 in order to protect from light.
Gentamicin 40 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, Ash Road North Wrexham LL13 9UF, 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 original package in order to protect from light.

## Gentamicin

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
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	Colourless, type I glass ampoules; 2 mL	4 years	Do not store above 25°C. Do not freeze.
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	Winthrop Pharmaceuticals UK Ltd, UK	PL 17780/0507	Vials; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin injection USP 10 mg/mL or 40 mg/mL	Health Canada	Teligent OU Estonia	2470462	Single-use ampoules; 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	Store below 25°C. Protect from light.
DBL gentamicin injection BP 80 mg/2 mL	TGA (Australia)	Hospira Australia Pty Ltd, Australia	AUST R 16337	Glass ampoules; 2 mL	Not specified	Store below 25°C.

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 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](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

Gentamicin injection from the following manufacturers are listed by UNICEF as approved sources for procurement<sup>3</sup>:

- Gland Pharma Ltd, India
- Intas Pharmaceuticals Ltd, India

It is recommended to check for updated information on the UNICEF website at the time of procurement.

## Related Products

Other formulations of gentamicin on the market include:

- 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)

---

<sup>3</sup> Available at [https://www.unicef.org/supply/index\\_27009.html](https://www.unicef.org/supply/index_27009.html)

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 EMLs.

## 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 pharmacopoeial 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-2. US Pharmacopoeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification (TLC)	The intensities and R <sub>f</sub> 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-3. British Pharmacopoeia 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 XI V
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 XI C
Sterility	Sterile	Ph.Eur. 2.6.1
Extractable volume	Comply	Ph.Eur. 2.9.17
Particulate matter	Comply	Ph.Eur. 2.9.19



# PART I: CLINICAL PARTICULARS

## Therapeutic indications

Gentamicin is a first-line treatment for community acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children.

Gentamicin injection is also indicated in urinary tract infections, chest infections, bacteremia, septicemia, severe neonatal infections, and other systemic infections due to sensitive organisms.

## Posology, method, and duration of administration

### Pneumonia<sup>1</sup>

#### Neonatal pneumonia

- 2.5 mg/kg IV every 8 hours (neonates <7 days: 2.5 mg/kg IV every 12 hours), together with amoxicillin 30 mg/kg IV every 12 hours for a total of at least 5 days

#### Pneumonia due to *Staphylococcus aureus* in children age 2 months–5 years

- 7.5 mg/kg IV in 1–3 divided doses daily, together with cloxacillin 25–50 mg/kg (maximum 2 g) orally every 6 hours for at least 3 weeks

#### Pneumonia in adults and children > 5 years

- Hospitalized patients
  - Adults: 5–7 mg/kg IV daily in divided doses, together with benzylpenicillin 2 million IU IV or IM every 4–6 hours for 7 days.
  - Children > 5 years: 7.5 mg/kg IV in 1–3 divided doses daily, together with benzylpenicillin 50,000–100,000 IU/kg (maximum 2 million IU) IV or IM every 4–6 hours for 7 days
- Patients with *atypical pneumonia* should *also* receive erythromycin 1 g (children: 10 mg/kg; maximum 1 g) IV every 6 hours for 14 days

#### Nosocomial pneumonia

- Adults: 5–7 mg/kg IV daily in divided doses for 7 days, supplemented by either cloxacillin 1–2 g IV every 6 hours or ceftazidime 1 g IV every 8 hours
- Children: 7.5 mg/kg IV in 1–3 divided doses daily for 7 days, supplemented by either cloxacillin 50 mg/kg (maximum 2 g) IV every 6 hours or ceftazidime 25 mg/kg (maximum 1 g) IV every 8 hours

<sup>1</sup> World Health Organization. 2001. *WHO Model Prescribing Information: Drugs used in Bacterial Infections*. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/en/d/js5406e/16.19.html#js5406e.16.19>.

- In hospitals with a high prevalence of methicillin-resistant *Staphylococcus aureus*, vancomycin 1 g (children: 20mg/kg; maximum 1 g) IV every 12 hours for 10–14 days should be added to the above regimens.

### Neonatal sepsis<sup>2</sup>

Gentamicin is delivered IV or by IM injection. The dosage of gentamicin is calculated based on patient weight to ensure the appropriate serum concentrations are obtained for safety and efficacy of the drug. Gentamicin has a narrow treatment window and incorrect usage can cause toxicity to the ears, kidneys, and neurological system. The recommended dose range for treatment of neonates is a total of 7.5 mg/kg/day, with one to three doses per day for seven to ten days. The WHO-recommended weight bands of gentamicin for inpatient treatment are summarized below.

WHO Recommended Gentamicin for Inpatient Treatment  
(All doses to be drawn from a 10 mg/ml stock concentration)

	LOW BIRTH WEIGHT, FIRST WEEK OF LIFE	NORMAL BIRTH WEIGHT, FIRST WEEK OF LIFE	WEEKS 2–4 OF LIFE
INFANT WEIGHT	(3 MG/KG IM OR IV ONCE DAILY)	(5 MG/KG IM OR IV ONCE DAILY)	(7.5 MG/KG IM OR IV ONCE DAILY)
1 ≤ 1.5 kg	0.3–0.5 mL	—	0.75–1.1 mL
1.5 ≤ 2 kg	0.5–0.6 mL	—	1.1–1.5 mL
2 ≤ 2.5 kg	0.6–0.75 mL	—	1.5–1.8 mL
2.5 ≤ 3 kg	—	1.25–1.5 mL	1.8–2.2 mL
3 ≤ 3.5 kg	—	1.5–1.75 mL	2.2–2.6 mL
3.5 ≤ 4 kg	—	1.75–2.0 mL	2.6–3.0 mL
4 ≤ 4.5 kg	—	2.0–2.25 mL	2.0–3.3 mL

### 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.

<sup>2</sup> PATH. 2015. *Gentamicin for Treatment of Neonatal Sepsis: A Landscape of Formulation, Packaging, and Delivery Alternatives*. Available at <https://path.org/resources/gentamicin-for-treatment-of-neonatal-sepsis-a-landscape-of-formulation-packaging-and-delivery-alternatives/>

### *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 (preferred) 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; therefore a reduced dosage is necessary where renal function is impaired.

## Contraindications

Hypersensitivity to the 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 should be monitored in these patients and serum levels determined so as 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 has usually reverted 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 1.6 of this annex, “[Pregnancy and lactation](#)”).

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 hypothermic 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 dyscrasias, purpura, stomatitis, convulsions, and effects on liver function occur occasionally.

Rarely, hypomagnesiemia 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 aid removal 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 consider the following particular 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 its suitable quality for use in medicinal product.

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	Chemistry
Gentamicin sulfate (monograph number 331)	Fujian Fukang Pharmaceutical Co, Ltd, CN 350 002 Fuzhou, China	R1-CEP 1998-155-Rev 08	10/20/2017	Chemistry

Other manufacturers of gentamicin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.<sup>3</sup>

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.

<sup>3</sup> 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

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 on 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 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 concern is the sterilization process together with the sterility of the facility where it is made.

The manufacturing process of gentamicin injection is a standard process—conducted under appropriate aseptic conditions—including 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 adsorption 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.

## 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 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 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<sup>®</sup> (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.



# 7.1% CHLORHEXIDINE DIGLUCONATE

SOLUTION OR GEL

## GENERAL PRODUCT INFORMATION

Chlorhexidine (digluconate or gluconate)<sup>1</sup> 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.

WHO has recognized chlorhexidine as a suitable antimicrobial for neonatal care. According to the WHO guideline for umbilical cord care, daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% free chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for newborns born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1,000 live births). Clean, dry cord care is recommended for newborns born in health facilities and at home in low neonatal mortality settings. Use of chlorhexidine in the low neonatal mortality settings does not significantly reduce the neonatal mortality rate, but may be considered only to replace application of a harmful traditional substance, such as cow dung, to the cord stump.

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

---

<sup>1</sup> 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 Pharmacopoeias, while *chlorhexidine gluconate* is used in the US Pharmacopoeia. *Chlorhexidine digluconate* is used throughout this document for precision and consistency.

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.

## 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. Procurers need to focus on product quality to ensure safety for the patient.

## 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% 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.

CHLORHEXIDINE 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.

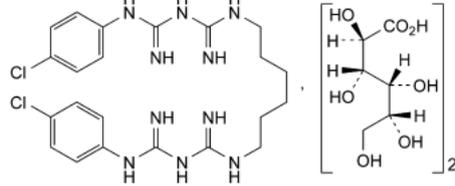
### Packaging and labeling

Since 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.

<b>Name of the Medicinal Product</b>	7.1% Chlorhexidine digluconate solution or gel for umbilical cord care
<b>Chemical Name</b>	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
<b>Chemical Structure</b>	<p><math>C_{34}H_{54}Cl_2N_{10}O_{14}</math>  <math>C_{22}H_{30}Cl_2N_{10}, 2C_6H_{12}O_7</math></p> 
<b>Pharmaceutical Form</b>	Topical solution—clear, colorless or pale yellow liquid Topical gel—colorless to yellow translucent gel
<b>Qualitative and Quantitative Composition</b>	<p><b>Solution</b></p> <p>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).</p> <p>Each 100 mL contains 7.1 g chlorhexidine digluconate equivalent to 4 g chlorhexidine.</p> <p>List of excipients:</p> <ul style="list-style-type: none"> <li>– Purified water</li> <li>– Sodium hydroxide</li> <li>– Benzalkonium chloride (optional)</li> </ul> <p><b>Gel</b></p> <p>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).</p> <p>Each sachet contains a 3-g dose containing 213 mg of chlorhexidine digluconate equivalent to 120 mg chlorhexidine.</p> <p>List of excipients<sup>2</sup>:</p> <ul style="list-style-type: none"> <li>– Purified water</li> <li>– Sodium acetate trihydrate</li> <li>– Guar gum</li> </ul>
<b>Packaging and Presentation</b>	<p>The WHO EMLc includes two presentations for umbilical cord care: 7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine.</p> <p>The 7.1% chlorhexidine digluconate solution is packaged in nozzle/dropper plastic bottle.</p> <p>The 7.1% chlorhexidine digluconate gel is packaged in foil laminate sachet or aluminum tube.</p>

<sup>2</sup> Based on the formulation of an innovator product, Umbipro®.

## 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 February 2018, there is only one SRA-approved product for 7.1% chlorhexidine digluconate for umbilical cord care, as shown in the below table.

Table CD-1. SRA-Approved Chlorhexidine Digluconate 7.1% Gel

SRA	PRODUCT NAME	SCIENTIFIC OPINION HOLDER*	REGISTRATION NUMBER	PACKAGING AND PRESENTATION
European Medicines Agency	Umbipro® 7.1% w/w gel	GlaxoSmithKline Trading Services Currabinny, Cork Ireland	EMEA/H/W/0037 99	3 g in a foil laminate sachet; pack sizes of a single sachet wallet or a 7-sachet carton

*\*Umbipro® received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) 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.*

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 other 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 product 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)

## 7.1% Chlorhexidine Digluconate

- 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:

- 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](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

7.1% Chlorhexidine digluconate solution or gel (delivering 4% chlorhexidine) from the following manufacturers are listed by UNICEF as approved sources for procurement<sup>3</sup>:

- Galentic Pharma (India) Pvt. Ltd, India
- Sirmaxo Chemicals Pvt Ltd, India
- Universal Corporation Ltd, Kenya

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.

---

<sup>3</sup> Available at [https://www.unicef.org/supply/index\\_27009.html](https://www.unicef.org/supply/index_27009.html).

## 7.1% Chlorhexidine Digluconate

- 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 an 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.
- 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—that is, 5.5–7.0.

## PRODUCT SPECIFICATIONS



7.1% chlorhexidine digluconate topical solution form must meet pharmacopoeial specifications,<sup>4</sup> such as those of the International Pharmacopoeia 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 pharmacopoeias 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. The testing parameters and acceptance criteria of the two pharmacopoeias are similar, with the exception that the assay and impurity limits are slightly different.

Table CD-2. International Pharmacopoeia 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
Identification b) Spectrophotometry	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
Identification 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
Assay	90.0–110.0%	1.14.4 High-performance liquid chromatography

<sup>4</sup> *Chlorhexidine digluconate* is used in the International Pharmacopoeia, while *chlorhexidine gluconate* is used in the British and US Pharmacopoeias.

## 7.1% Chlorhexidine Digluconate

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-3. US Pharmacopoeia 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>
Identification b) TLC	The principal spot from the Sample solution corresponds in color, size, and R <sub>f</sub> value to that from the standard solution.	USP<201>
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-4. British Pharmacopoeia Specifications for Chlorhexidine Digluconate Topical Gel

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Spectrophotometry	The light absorption of the resulting solution in the range 200–320 nm exhibits two maxima, at about 231 nm and 255 nm; and two minima, at 222 nm and 242 nm.	Appendix II B
Identification b) Reaction with bromine water	A reddish-yellow color is produced.	As per BP monograph of chlorhexidine gluconate gel
Identification c) HPLC	The chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to chlorhexidine in the chromatogram obtained with solution (1).	HPLC, Appendix III D
pH	5.0–7.0	Appendix V L
Assay	95.0–105.0%	HPLC, Appendix III D
Impurities (4-chloroaniline)	Not more than 20 ppm	Gas chromatography, Appendix III B

## 7.1% Chlorhexidine Digluconate

Table CD-5. US Pharmacopoeia 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>
Identification 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>
Identification c) TLC	The principal spot of the sample solution corresponds in color, size, and R <sub>f</sub> 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 sachet, the seal integrity test as in-process control should be considered.



## PART I: 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. 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  $\geq 1/10$
- Common  $\geq 1/100$  to  $< 1/10$
- Uncommon  $\geq 1/1,000$  to  $< 1/100$
- Rare  $\geq 1/10,000$  to  $< 1/1,000$
- Very rare  $< 1/10,000$
- 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.

## 7.1% Chlorhexidine Digluconate Annex

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, there no WHO-prequalified chlorhexidine digluconate solution exists.

Four manufacturers of chlorhexidine digluconate solution have obtained a certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming suitable quality for use in medicinal product.

Manufacturers of Chlorhexidine Digluconate Solution API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Chlorhexidine digluconate solution (monograph number 658)	R.N. Laboratories IN 400 053 Mumbai, India	R1-CEP 2006-171-Rev 01	10/30/2013	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Dishman Biothek Ltd IN 380 009 Ahmedabad, India	R1-CEP 2003-094-Rev 03	10/10/2017	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Evonik Technochemie GMBH DE 69221 Dossenheim, Germany	R1-CEP 2001-343-Rev 03	11/8/2013	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Medichem, S.A. ES 08970 Sant Joan Despí, Spain	R1-CEP 1993-009-Rev 04	2/16/2009	Chemistry
Chlorhexidine digluconate solution DCG (monograph number 658)	Medichem, S.A. ES 08970 Sant Joan Despí, Spain	R0-CEP 2017-128-Rev 00	04/08/2017	Chemistry

Other manufacturers of chlorhexidine digluconate solution should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.<sup>1</sup>

Chlorhexidine digluconate solution must meet pharmacopoeia specifications,<sup>2</sup> 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.

## 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.

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)

The quality of excipients should be compliant with recognized pharmacopoeias (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.<sup>3</sup> 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

<sup>1</sup> 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.

<sup>2</sup> *Chlorhexidine digluconate* is used in the International and European Pharmacopoeias, while *chlorhexidine gluconate* is used in the US Pharmacopoeia.

<sup>3</sup> EMA assessment report of Umbipro®.

the 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<sup>4</sup> 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 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 as 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.

---

<sup>4</sup> PATH. 2010. "Stability Data of Chlorhexidine Formulations: PATH Summary." PATH: Seattle.

## 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.

### 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.

## 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.

An appropriate comparator product is Umbipro<sup>®</sup> (chlorhexidine digluconate 7.1% gel, delivering 4% chlorhexidine, GlaxoSmithKline). The composition of the proposed product should be the same as the comparator product.

# 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 dispersible amoxicillin as the recommended first line treatment for pneumonia in children under five.<sup>1</sup> Amoxicillin 250 mg dispersible tablet is included in the WHO Essential Medicines List and Priority Medicines List for Children.<sup>2</sup> It is also considered an essential medicine for child health by the UN Commission on Life-Saving Commodities for Women and Children.

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.

---

<sup>1</sup> 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/](http://www.who.int/maternal_child_adolescent/documents/child-pneumonia-treatment/en/).

<sup>2</sup> 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/](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 as.

## 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.

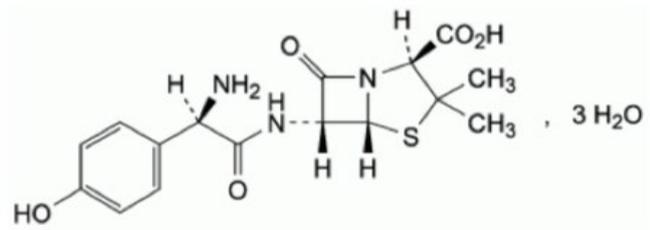
Additional information about packaging and labeling can be found in the Annex.

**Storage, transportation, and distribution**

Procurers need to verify from manufacturers 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).

## Amoxicillin

<b>Name of the Medicinal Product</b>	Amoxicillin 250-mg dispersible tablets
<b>Chemical Name</b>	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
<b>Chemical Structure</b>	$C_{16}H_{19}N_3O_5S, 3H_2O$ 
<b>Pharmaceutical Form</b>	Dispersible tablets
<b>Qualitative and Quantitative Composition</b>	Each tablet contains amoxicillin trihydrate equivalent to 250 mg amoxicillin. List of typical excipients <sup>3</sup> : <ul style="list-style-type: none"> <li>– Aspartame</li> <li>– Colloidal anhydrous silica</li> <li>– Magnesium stearate</li> <li>– Microcrystalline cellulose</li> <li>– Crospovidone</li> <li>– Other sweeteners</li> <li>– Flavors</li> </ul>
<b>Packaging and Presentation</b>	Amoxicillin dispersible tablets are usually packed in blisters (aluminum/PVC) or strips (aluminum) of 10 tablets.

<sup>3</sup> Based on the formulation of amoxicillin dispersible tablets approved by EMA and MHRA, although for different strengths.

## 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 is not included in the WHO PQP. Therefore, no WHO-prequalified amoxicillin products are available.

### SRA-approved products

As of February 2018, no SRA-approved amoxicillin 250-mg dispersible tablets are found.<sup>4</sup>

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](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>

---

<sup>4</sup> Other strengths of amoxicillin dispersible tablets (e.g., 750 mg, 1,000 mg) are found approved and marketed in SRA countries, and are indicated for treatment of various bacterial infection.

## Trusted sources

Amoxicillin 250 mg dispersible tablets from the following manufacturers are listed by UNICEF as approved sources for procurement<sup>5</sup>:

- Medopharm Private Ltd, India
- Medreich Plc, United Kingdom
- Micro Labs Ltd, India
- Remedica Ltd, Cyprus
- Sandoz d.d, Slovenia

In addition, PT Sanbe Farma, Indonesia, is certified GMP-compliant by WHO PQP for its production amoxicillin 250 mg dispersible tablets.<sup>6</sup>

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.

<b>Amoxicillin caps</b>	<ul style="list-style-type: none"> <li>– Amoxicillin capsules are the most widely available pharmaceutical form, available in strengths of 125 mg–1,000 mg.</li> <li>– It is the preferred formulation for adults and can be taken without water if necessary.</li> </ul>
<b>Amoxicillin tabs</b>	<ul style="list-style-type: none"> <li>– Amoxicillin tablets are another conventional form, often available with scoring, available in strengths of 500 mg–1,000 mg.</li> <li>– Scored tablets allow pharmaceutical tablets to be broken and dosing adjusted according to prescription.</li> <li>– They are not as extensively used as capsules and often need to be taken with water.</li> </ul>
<b>Amoxicillin OS</b>	<ul style="list-style-type: none"> <li>– Amoxicillin powder for oral suspension is at present the most commonly used pediatric formulation.</li> <li>– It is administered as a liquid which facilitates the treatment of children and those with difficulties swallowing solid dosage forms like tablets or capsules.</li> <li>– It is available in the strengths of 125 mg/5 mL to 500 mg/5 mL.</li> </ul>

<sup>5</sup> Available at

[https://www.unicef.org/supply/files/Amoxicillin\\_DT\\_Product\\_Profile\\_and\\_Supply\\_Update.pdf](https://www.unicef.org/supply/files/Amoxicillin_DT_Product_Profile_and_Supply_Update.pdf).

<sup>6</sup> Available at [https://extranet.who.int/prequal/sites/default/files/WHOPIR\\_PT-Sanbe20-21February2017.pdf](https://extranet.who.int/prequal/sites/default/files/WHOPIR_PT-Sanbe20-21February2017.pdf).

In the WHO Model List of Essential Medicines for Children, the following dosage forms for amoxicillin are listed<sup>7</sup>:

- 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 term 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 greater dosage accuracy compared to oral suspension, which has 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.

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.

---

<sup>7</sup> For use as first choice for treatment of community acquired pneumonia (mild to moderate), community-acquired pneumonia (severe), complicated severe acute malnutrition, lower urinary tract infections, otitis media, pharyngitis, sepsis in neonates and children, sinusitis, and uncomplicated severe acute malnutrition.

## PRODUCT SPECIFICATIONS



The product must meet the USP specifications,<sup>8</sup> 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-I. US Pharmacopoeia Specifications for Amoxicillin Dispersible Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification: TLC	The R <sub>f</sub> 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

<sup>8</sup> As of February 2018, there are no monographs of amoxicillin dispersible tablets published in the International and British Pharmacopoeias. Please check updated information at <http://apps.who.int/phint/en/p/about/> and in the British Pharmacopoeia.



## PART I: CLINICAL PARTICULARS

### Therapeutic indications

WHO recommends oral amoxicillin as the first-line 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 bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Acute cystitis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- Helicobacter pylori eradication
- Lyme disease

Oral amoxicillin is also indicated for the prophylaxis of endocarditis.

### Posology, method, and duration of administration

Doses of Amoxicillin for Children 2–59 Months of Age with Pneumonia

CATEGORY OF PNEUMONIA	AGE/WEIGHT OF CHILD	DOSAGE OF AMOXICILLIN DISPERSIBLE 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.

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  $\geq$  40 kg**Recommended Doses for Adults and Children  $\geq$  40 Kg

INDICATION*	DOSE
Acute bacterial sinusitis, acute pyelonephritis, dental abscess with spreading cellulitis, and acute cystitis	250–500 mg every 8 hours, 750 mg–1 g every 12 hours For severe infections 750 mg–1 g every 8 hours Acute cystitis may be treated with 3-g twice daily for 1 day
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) 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**

Recommended Doses for Renal Impairment

GFR (ML/MIN)	CHILDREN < 40 KG*	ADULTS AND CHILDREN $\geq$ 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.

Recommended Dose for Adults and Children  $\geq$  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 in order 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 ( $\geq 1/10$ )
- Common ( $\geq 1/100$  to  $< 1/10$ )
- Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )
- Very rare ( $< 1/10,000$ )
- 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 thrombocytopenia, 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 pseudomembranous 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 not included in the WHO PQP. Therefore, there is no WHO-prequalified amoxicillin API.

Several manufacturers of amoxicillin API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Manufacturers of Amoxicillin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
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 01	4/26/2017	Chemistry
Amoxicillin trihydrate (monograph number 260)	Sun Pharmaceutical Industries Ltd IN 400 063 Mumbai, India	R1-CEP 1997-028-Rev 04	5/29/2015	Chemistry
Amoxicillin trihydrate, compacted (monograph number 260)	Zhuhai United Laboratories Co, Ltd CN 519 040 Sanzao Town, China	R1-CEP 2007-191-Rev 02	4/26/2017	Chemistry
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	Chemistry
Amoxicillin trihydrate, compacted (monograph number 260)	North China Pharmaceutical Group Semisyntech Co, Ltd CN 052 165 Shijiazhuang, China	R1-CEP 2009-329-Rev 00	3/17/2015	Chemistry
Amoxicillin trihydrate (monograph number 260)	Aurobindo Pharma Ltd IN 500 038 Hyderabad, India	R1-CEP 2007-147-Rev 03	10/3/2017	Chemistry

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Amoxicillin trihydrate (monograph number 260)	Oman Chemicals and Pharmaceuticals L.LC OM 512 Al Buraimi, Oman	R1-CEP 1996-060-Rev 03	12/20/2010	Chemistry
Amoxicillin trihydrate (monograph number 260)	Antibióticos de León SLU ES 24009 León, Spain	R1-CEP 2001-123-Rev 03	2/16//2015	Chemistry
Amoxicillin trihydrate, compacted (monograph number 260)	CSPC Zhongnuo Pharmaceutical (Shijiazuang) Co Ltd CN 050 041 Shijiazhuang, China	R1-CEP 2012-245-Rev 00	1/26/2018	Chemistry
Amoxicillin trihydrate (monograph number 260)	GlaxoSmithKline Research & Development Ltd, GB TW8 9GS London, UK	R1-CEP 2000-010-Rev 03	3/25/2014	Chemistry
Amoxicillin trihydrate (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R1-CEP 2004-074-Rev 00	4/30/2013	Chemistry
Amoxicillin trihydrate (monograph number 260)	Teva Pharmaceutical Industries Ltd IL 49131 Petach Tikva, Israel	R1-CEP 2004-146-Rev 01	8/1/2013	Chemistry
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	Chemistry
Amoxicillin trihydrate (monograph number 260)	United Laboratories (Inner Mongolia) Co Ltd CN 015 000 Bayannaouer, China	R0-CEP 2012-078-Rev 02	2/8/2016	Chemistry
Amoxicillin trihydrate (monograph number 260)	CSPC Zhongnuo Pharmaceutical (Shijiazuang) Co Ltd CN 050 041 Shijiazhuang, China	R1-CEP 2004-147-Rev 00	4/22/2013	Chemistry
Amoxicillin trihydrate Almería, Spain (monograph number 260)	DSM Sinochem Pharmaceuticals Netherlands B.V. NL 2613 AX Delft, The Netherlands	R1-CEP 2001-367-Rev 04	2/5/2015	Chemistry
Amoxicillin trihydrate Enzymatic process (monograph number 260)	Aurobindo Pharma Ltd IN 500 038 Hyderabad, India	R0-CEP 2017-037-Rev 00	12/6/2017	Chemistry
Amoxicillin trihydrate Enzymatic process (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R0-CEP 2014-220-Rev 01	1/5/2017	Chemistry
Amoxicillin trihydrate Toansa, India (monograph number 260)	DSM Sinochem Pharmaceuticals Netherlands B.V. NL 2613 AX Delft, The Netherlands	R1-CEP 2007-226-Rev 01	10/17/2014	Chemistry

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Amoxicillin trihydrate Enzymatic process (monograph number 260)	GlaxoSmithKline Research and Development Ltd GB UB11 1BT Stockley Park, UK	R0-CEP 2015- 064-Rev 01	9/28/2017	Chemistry
Amoxicillin trihydrate Enzymatic process, compacted (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R0-CEP 2017- 009-Rev 00	4/6/2017	Chemistry

Other manufacturers of amoxicillin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.<sup>1</sup>

Amoxicillin 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.

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 less than 30%—most preferably from 10% to 20%.

## 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 pharmacopoeial 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.

<sup>1</sup> 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.

## Manufacturing process

The amoxicillin dispersible tablets should be manufactured using dry granulation or the direct compression method. A wet granulation method is not recommended because the formulation is highly sensitive to moisture and temperature conditions.

## Packaging

Amoxicillin dispersible tablets are usually packed in blisters (aluminum/PVC) or strips (aluminum).

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

### Safety

- Declarations as to 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  $37 \pm 1^\circ\text{C}$  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  $37 \pm 1^\circ\text{C}$  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

Pharmacopoeial 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 the comparator product or be present in other products which contain the same API as the multisource product and which 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.

## EMA guidance on the evaluation of taste marking<sup>2</sup>

### 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.
- 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.

---

<sup>2</sup> 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](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf).

- 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 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 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.

In order 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 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 has to 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 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.”

# 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 they are intended 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.<sup>1,2</sup> 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.

---

<sup>1</sup> World Health Organization. 2005. *The Treatment of Diarrhea: A Manual for Physicians and other Senior Health Workers*. Geneva: WHO. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241593180/en/](http://www.who.int/maternal_child_adolescent/documents/9241593180/en/).

<sup>2</sup> 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 [http://www.who.int/maternal\\_child\\_adolescent/documents/9241594217/en/](http://www.who.int/maternal_child_adolescent/documents/9241594217/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. 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, instead of the previous standard ORS with a total osmolarity of 311 mOsm/L, due to greater effectiveness.

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 product can be affected by highly humid environmental conditions. A compound of polyethylene (inside), aluminum (middle), and polyester or any other suitable coating compound (outside) has proven to be a satisfactory combination for packing ORS. However, product stability also depends on these conditions: the raw material is dry, the sealing is perfect, and the final product is stored appropriately.

ORS should be procured with packaging designated with: (1) the total net mass and the mass of the contents of each constituent, 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 also 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 <sub>6</sub> H <sub>12</sub> O <sub>6</sub>	13.5
Potassium chloride	KCl	1.5
Trisodium citrate, dihydrate	C <sub>6</sub> H <sub>5</sub> Na <sub>3</sub> O <sub>7</sub> ·2H <sub>2</sub> O	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.<sup>3</sup> The WHO

<sup>3</sup> Loo, D. M. I., 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.

**Packaging and Presentation**

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.<sup>4</sup> The results of these studies showed 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.

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 compound of polyethylene (inside), aluminum (middle), and polyester or any other suitable coating compound (outside) has proved to be a satisfactory combination 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; in order 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

---

<sup>4</sup> Available at

[http://apps.who.int/iris/bitstream/handle/10665/69227/WHO\\_FCH\\_CAH\\_06.1.pdf;jsessionid=A426B006186DD09F4F593604F6D66435?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/69227/WHO_FCH_CAH_06.1.pdf;jsessionid=A426B006186DD09F4F593604F6D66435?sequence=1)

## 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 February 2018, there are no ORS products approved in SRA countries in the same formulation and strength as that described in the “[Product Specifications](#)” section.<sup>5</sup>

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, 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, 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>
- EU regulatory authorities: [https://ec.europa.eu/health/documents/community-register/regca\\_en](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>

---

<sup>5</sup> 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.

## Trusted sources

ORS from the following manufacturers is listed by UNICEF as approved sources for procurement<sup>6</sup>:

- CHI Pharmaceuticals, Nigeria
- FDC Ltd, India
- KBI, Germany
- Renata Ltd, Bangladesh
- Universal Corporation Ltd, Kenya

It is recommended to check for updated information on the UNICEF website at the time of procurement.

## Related products

ORS products approved in the UK<sup>7</sup> 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. It is available in a sachet for 200 mL. When dissolved in 200 mL of water, each ORS sachet will 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<sup>8</sup> 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. It is available in a sachet for 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.<sup>9</sup> 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.

---

<sup>6</sup> Available at

[https://www.unicef.org/supply/files/Amoxicillin\\_DT\\_Product\\_Profile\\_and\\_Supply\\_Update.pdf](https://www.unicef.org/supply/files/Amoxicillin_DT_Product_Profile_and_Supply_Update.pdf).

<sup>7</sup> <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1512713009284.pdf>

<sup>8</sup> <http://tga-search.clients.funnelback.com/s/search.html?query=oral+rehydration+salt&collection=tga-artg&profile=record>.

<sup>9</sup> World Health Organization. 2002. “New Formula Oral Rehydration Solution.” In *WHO Drug Information*. Vol. 16, No. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/en/d/js4950e/2.4.html>.

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,  $\text{NaHCO}_3$  (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,  $\text{C}_6\text{H}_{12}\text{O}_6 \cdot \text{H}_2\text{O}$ , 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 as a result of heat/humidity if it is properly manufactured, packaged, and sealed.

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 in excess of 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 pharmacopoeial specifications, such as those of the International Pharmacopoeia, 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 pharmacopoeias are similar. USP and BP monographs are applicable for ORS formulations containing sodium bicarbonate or sodium citrate, whereas International Pharmacopoeia is applicable only for ORS formulations containing trisodium citrate.

Table ORS-I. International Pharmacopoeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
<b>Identification</b>		
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 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
<b>Assays</b>		
a) Sodium	90–110%	1.8 Atomic spectrometry: emission and absorption
b) Potassium	90–110%	1.8 Atomic spectrometry: emission and absorption
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

Oral Rehydration

Table ORS-2. US Pharmacopoeia Specifications for ORS

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
<b>Identification</b>		
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
<b>Assay</b>		
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
Minimum Fill	The average net weight of the contents of the 10 containers is 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 1 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 1 of the 30 containers is less than 95% but	USP<755>

## Oral Rehydration

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	NLT 90% of the labeled amount, or more than 105% but NMT 110% of the labeled amount.	
pH of the reconstituted solution	7.0–8.8	USP<791>
Loss on drying	At 50°C, NMT 1.0%	USP<731>

Table ORS-3. British Pharmacopoeia 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) Potassium	90–110%	Appendix II D
b) Sodium	90–110%	Appendix II D
c) Chlorides	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	Appendix XII C

## Oral Rehydration

Additional tests for the ORS products as recommended by WHO are listed below:

### **Seal (only if packed in aluminum laminate)**

As 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.



# PART I: 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:

- 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<sup>1</sup>

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 pharmacopoeial 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 pharmacopoeial 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 pharmacopoeial 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.

---

<sup>1</sup> 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](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 in view of the fact that this quality 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 of crystallization in both ingredients eventually leads to a 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 pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

If sodium citrate is produced locally, but is not of the mentioned pharmaceutical grade, the standard for food grade 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 medicines 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.

Excipient 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 in excess of 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 in order 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 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, with its tendency to caramelize rapidly in humidity and heat, requires almost daily cleaning of the mixing machine.
- 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 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.

## 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 compound of polyethylene, aluminum, and polyester (or any other suitable coating compound) has proved to be a satisfactory combination 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<sup>2</sup>
- Middle: aluminum (ALU) 0.009–0.015 mm or 24.3–40.5 g/m<sup>2</sup>
- Outside: polyester (P) 0.012–0.015 mm or 12.9–20.9 g/m<sup>2</sup>

Choice of the recommended compound does not guarantee a stable and satisfactory product if the raw material is not dry, the sealing is imperfect, and 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.

ORS-citrate does not absolutely require an impermeable packaging material. If packed in polyethylene it may, however, absorb moisture and some lumping, which is usually acceptable.

The possibilities for the use of polyethylene packets are basically 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.<sup>1,2</sup> 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, essentially 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 salt of zinc, 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 could 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 the ease of administration and logistics.

---

<sup>1</sup> WHO. 2005. *The Treatment of Diarrhea: A Manual for Physicians and Other Senior Health Workers*. Geneva: WHO. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241593180/en/](http://www.who.int/maternal_child_adolescent/documents/9241593180/en/).

<sup>2</sup> WHO. 2006. *Implementing the New Recommendations on the Clinical Management of Diarrhea: Guidelines for Policy Makers and Programme Managers*. Geneva: WHO. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241594217/en/](http://www.who.int/maternal_child_adolescent/documents/9241594217/en/).

A strong safety profile allows the potential classification of zinc as an over-the-counter drug, without requiring a prescription.

## 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 as.

## 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.<sup>3,4</sup>

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

### **Storage, transportation, and distribution**

Procurers need to verify from manufacturers 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 requirement can be found in Section 3.

### **Other specific requirements**

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

---

<sup>3</sup> 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.

<sup>4</sup> Batchelor, H. K., and J. F. Marriott. 2015. "Formulations for Children: Problems and Solutions." *British Journal of Clinical Pharmacology* 79(3): 405–18.

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.

**Name of the Medicinal Product**

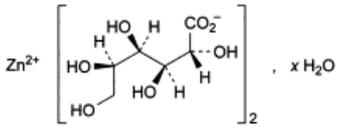
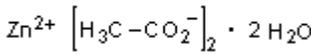
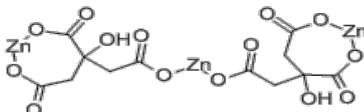
Zinc (sulfate, gluconate, acetate, citrate)

**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 of hydration. 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<sup>5</sup>:

- Aspartame
- Colloidal anhydrous silica
- Magnesium stearate
- Microcrystalline cellulose
- Crospovidone
- 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

<sup>5</sup> Based on the formulation of the WHO-prequalified products.

## 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 February 2018, there are three 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/prequal/content/prequalified-lists/medicines>.

Table Z-I. List of WHO-Prequalified Zinc Sulfate Dispersible Tablets

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 Pharmaceutiqu es Rodael, 1 route de SOCX, Bierne, 59380, France  API manufacturing site: Dr Paul Lohmann GmbH KG, Hauptstrasse 2, Emmerthal, 31860, Germany	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.
DI004	Alkem Laboratories Ltd, Alkem House, "Devashish" Senapati Bapat Marg, Lower Parel, Mumbai, 400 013, India	FPP manufacturing site: Alkem Laboratories Ltd, 167/2 Mahatma Ghandi Udyog Nagar, Amaliya, Dhabel, Daman, 396 210, India  API manufacturing site: Canton Laboratories Pvt Ltd, Survey No. 350, Mujpur, Taluka: Padra, Vadodara, Gujarat, 391440, India	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC: 10 x 10's	19-Feb-14	36 months	Do not store above 30°C, protect from moisture, protect from light.

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
D1005	Macleods Pharmaceuticals Ltd, 304 Atlanta Arcade, Marol Church Road, Anheri-Kurla Road, Anheri (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	36 months	Do not store above 30°C, protect from moisture, protect from light.
		API manufacturing site: Dr Paul Lohmann GmbH KG, Hauptstrasse 2, 31860 Emmerthal, Germany;					
		Canton Laboratories Pvt Ltd, Survey No. 350, Mujpur, Taluka: Padra, Vadodara, Gujarat, 391440, India					

## SRA-approved products

As of February 2018, there are no SRA-approved zinc supplements for use in treatment of diarrhea in children,<sup>6</sup> 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>
- EU regulatory authorities: [https://ec.europa.eu/health/documents/community-register/regca\\_en](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-I above, zinc sulfate 20 mg dispersible tablets from the following manufacturers are listed by UNICEF as approved sources for procurement<sup>7</sup>:

- CHI Pharmaceuticals, Nigeria
- FDC Ltd, India
- Square Pharmaceuticals, Bangladesh
- Universal Corporation Ltd, Kenya

It is recommended to check for updated information on the UNICEF website at the time of procurement.

---

<sup>6</sup> Zinc supplements approved and marketed in SRA countries are of different strengths and to be used for the treatment of zinc deficiency.

<sup>7</sup> Available at [https://www.unicef.org/supply/files/ORS\\_and\\_Zinc\\_Supply\\_Update.pdf](https://www.unicef.org/supply/files/ORS_and_Zinc_Supply_Update.pdf)

### 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 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 pharmacopoeial specifications,<sup>8</sup> 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,<sup>9</sup> 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 in order 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.

---

<sup>8</sup> As of February 2018, there are no monographs of zinc tablets and zinc oral solutions published in the International Pharmacopoeia. Updated information should be checked at <http://apps.who.int/phint/en/p/about/>

<sup>9</sup> World Health Organization. 2007. *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers*. Geneva: WHO. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241594942/en/](http://www.who.int/maternal_child_adolescent/documents/9241594942/en/)

## Zinc

Table Z-2. US Pharmacopoeia Specifications for Zinc Sulfate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	A white precipitate is formed. When an additional 2 mL of <i>sodium hydroxide solution</i> is added, the precipitate dissolves. When 10 mL of <i>ammonium chloride solution</i> is added, the solution remains clear. When 0.1 mL of <i>sodium sulfide solution</i> is added, a white precipitate is formed.	As per USP monograph of zinc sulfate tablets
Identification b) Sulfate	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-3. British Pharmacopoeia Specifications for Zinc Sulfate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Yields the reactions characteristics of zinc and zinc salts.	Appendix VI
Identification b) Sulfate	Yields the reactions characteristics 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

Table Z-4. US Pharmacopoeia Specifications for Zinc Sulfate Oral Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Meet the requirements	USP<191>
Identification b) Sulfate	Meet 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>

## Zinc

Table Z-5. US Pharmacopoeia Specifications for Zinc Gluconate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) TLC	The principal spot from <i>sample solution</i> corresponds in color, size, and Rf value to that from the <i>standard solution</i> .	As per USP monograph of zinc gluconate tablets
Identification b) Chemical reaction	A white precipitate is formed after the first addition of <i>sodium hydroxide solution</i> . The precipitate dissolves after the second addition of <i>sodium hydroxide solution</i> . The solution remains clear after addition of <i>ammonium chloride solution</i> , and a white precipitate forms after addition of <i>sodium sulfide solution</i> .	As per USP monograph of zinc gluconate tablets
Assay (zinc gluconate)	93.0–107.0%	Titration, USP monograph
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	Meet the requirements	USP<905>

Table Z-6. US Pharmacopoeia Specifications for Zinc Acetate Oral Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Meet the requirements	USP<191>
Identification b) Acetate	Meet 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 <i>Escherichia coli</i>	USP<62>

## WHO guidance on the study for the scored tablets<sup>10</sup>

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 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 uniformity of content is determined by measuring the content of each of 10 halves using the assay method described in the US or British Pharmacopoeia. 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 uniformity of content test, each half 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.

---

<sup>10</sup> 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.



## PART I: 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: ½ tablet once daily for 10–14 days

For children 6 months–5 years of age: 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.

### 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.

### 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.

## 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 ( $\geq 10\%$ ) and regurgitation was reported commonly ( $\geq 1\%$  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).

## 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, 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 particular 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 February 2018, there are two zinc sulfate APIs prequalified by the WHO PQP.

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 25°C.	60 months	12/7/2016
WHOAPI-232	Dr Paul Lohmann GmbH KG	Dr Paul Lohmann GmbH KG, Hauptstrasse 2 31860 Emmerthal Germany	Do not store above 30°C; protect from moisture.	36 months	7/3/2014

Two manufacturers of zinc have obtained a certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

## Manufacturers of Zinc 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	2/1/2017	Chemistry
Zinc gluconate (monograph number 2164)	Givaudan-Lavirotte FR, 69008 Lyon, France	R0-CEP 2012-221-Rev 00	2/7/2014	Chemistry

Other manufacturers of zinc should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.<sup>1</sup>

API specifications of zinc should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP) with additional tests/limits for arsenic; as well as for lead, alkalies, and alkaline earths and iron if not included in that monograph. Such additional tests may be based on another pharmacopoeial 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 croscopovidone), 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)*,<sup>2</sup> 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).

<sup>1</sup> 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.

<sup>2</sup> World Health Organization/Prequalification Team. 2016. *Q&A: Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution)*. Geneva: WHO/PQT. Available at [https://extranet.who.int/prequal/sites/default/files/documents/50%20Q%26A%20zinc%20sulfate%20tablets\\_Nov2016.pdf](https://extranet.who.int/prequal/sites/default/files/documents/50%20Q%26A%20zinc%20sulfate%20tablets_Nov2016.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 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 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.

## 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 in order to improve acceptability but these substances “should not impair the bioavailability or the therapeutic efficacy or safety of the preparation.” In order 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 1 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 ( $n \geq 6$ ) 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 marking<sup>3</sup>**

### **Qualitative evaluation of the taste by a taste panel<sup>4</sup>**

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 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.

---

<sup>3</sup> 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,.

<sup>4</sup> 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](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf)

## 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.
- 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) could 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.

In order 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<sup>5</sup>

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,<sup>6</sup> 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.

---

<sup>5</sup> 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.

<sup>6</sup> To identify a  $\pm 7.5\%$  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).