7.1% CHLORHEXIDINE DIGLUCONATE

SOLUTION OR GEL

GENERAL PRODUCT INFORMATION

Chlorhexidine (digluconate or gluconate)[1] is a broad-spectrum antiseptic. It has been widely used in a range of applications including wound care, hand washes, preoperative body shower, oral hygiene, and general disinfection.

According to the WHO guideline for umbilical cord care and the WHO guideline for recommendations on maternal and newborn care for a positive postnatal experience, chlorhexidine is recommended to the umbilical cord stump for the prevention of neonatal infection. The applications are for clean, dry umbilical cord care (recommended) and in settings where harmful traditional substances (e.g. animal dung) are commonly used on the umbilical cord, for the daily application of 4% chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) to the umbilical cord stump in the first week after birth (context-specific recommendation).Chlorhexidine is identified by the UN Commission on Life-Saving Commodities for Women and Children as one of 13 lifesaving commodities for women and children. The gel form of 7.1% chlorhexidine digluconate is proven to be as effective as the solution form. Chlorhexidine, both gel and solution, is included in the WHO Model List of Essential Medicines for Children (EMLc) under Specific Medicines for Neonatal Care. This is a higher concentration than the 5% chlorhexidine digluconate (delivering 2.8% chlorhexidine) listed on the EMLc as an antiseptic.

This document focuses on the presentation used for the umbilical cord care according to the WHO EMLc which is 7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine.

[1] It is common practice to use chlorhexidine gluconate and chlorhexidine digluconate interchangeably when referring to the chlorhexidine solution. Chlorhexidine digluconate is used in the European and International Pharmacopeias, while chlorhexidine gluconate is used in the US Pharmacopeia. Chlorhexidine digluconate is used throughout this document for precision and consistency.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procure only 7.1% chlorhexidine digluconate solution or gel for umbilical cord care that is produced by cGMP-compliant pharmaceutical manufacturers. 7.1% chlorhexidine digluconate solution or gel for umbilical cord care is considered a medicine by inclusion in the WHO EML, and therefore, procurement should be based on the product quality.

2. Chlorhexidine that is procured for umbilical cord care should be specifically formulated as topical medicine, which is different in strength from other pharmaceutical and non-pharmaceutical products containing chlorhexidine digluconate, such as presurgical and oral antiseptics, surface disinfectants, and hand sanitizers.

3. The product should not contain alcohol. Topically applied products containing ethanol alcohol may cause percutaneous toxicity in the newborn.

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

5. WHO[2] has issued an alert on multiple recent reports of eye injury, including blindness, with the use of chlorhexidine gluconate 7.1%. This product may cause serious harm if mistakenly applied to the eyes, therefore the following recommendations were provided:

   - Select the optimal primary container/dosage form for chlorhexidine gluconate 7.1% or modify the design of the container to distinguish the product from other medicines typically used for newborns.
   - The product label should be updated with appropriate information on the safe use of the product. More detailed instructions for users (flyers, posters, pictorials etc.) that are culturally appropriate and easy to understand are recommended to avoid misuse of the product.

KEY QUALITY CONSIDERATIONS

Product specification

7.1% chlorhexidine digluconate solution or gel for umbilical cord care products must comply with the quality specifications as detailed in section 4.

Chlorhexidine for umbilical cord care should be procured in a concentration of 7.1% chlorhexidine digluconate, delivering 4% free chlorhexidine. There is common confusion regarding the concentrations of chlorhexidine digluconate versus free chlorhexidine. The conversion between the two is listed in the table below. It is important to note that the WHO EMLc also includes 5% chlorhexidine digluconate as an antiseptic, which delivers only 2.8% free chlorhexidine, a lower level than is recommended for umbilical cord care.

[2] https://www.who.int/news/item/28-08-2020-chlorhexidine-7-1-digluconate-(chx)-aqueous-solution-or-gel-(10ml)-reports-of-serious-eye-injury-due-to-errors-in-administration

Procurers should be aware of the difference between chlorhexidine digluconate and free chlorhexidine and not misunderstand that the "5% chlorhexidine digluconate" listed on the EMLc for antiseptic is higher or more effective than 4% free chlorhexidine.

Table CD-1: Equivalency of Free Chlorhexidine from Chlorhexidine Digluconate

CHLOROHEXIDINE DIGLUCONATE	EQUIVALENT TO FREE CHLORHEXIDINE	NOTES
20.0%	11.3%	20.0% chlorhexidine digluconate will deliver 11.3% free chlorhexidine. 20% chlorhexidine digluconate is the concentration of API used for manufacture of chlorhexidine topical solution and gel.
7.1%	4.0%	7.1% chlorhexidine digluconate will deliver 4.0% free chlorhexidine. 7.1% chlorhexidine digluconate is the concentration of FPP listed on the EMLc for umbilical cord care.
5.0%	2.8%	5.0% chlorhexidine digluconate will deliver 2.8% free chlorhexidine. 5.0% chlorhexidine digluconate is the concentration of FPP listed on the EMLc for antiseptic.

Only two dosage forms—solution or gel—of 7.1% chlorhexidine digluconate should be procured. Both solution and gel are equally effective for umbilical cord care. Selection of the dosage form (solution or gel) will depend on: which form is most acceptable to mothers, caregivers, skilled providers, and others who are likely to use the product; product availability (e.g., ease of production/import and supply sustainability); and an evaluation of the primary containers for the selected dosage form.

Chlorhexidine digluconate may be available in other concentrations and dosage forms, such as cream or lotion. However, the human body might absorb chlorhexidine gluconate from these dosage forms differently than from the solution or gel forms. In addition, the shelf life and compatibility with other ingredients could be adversely affected when dosage forms are changed.

Procure only a formulation of 7.1% chlorhexidine digluconate that does not contain alcohol. Use of alcohol might cause pain or a burning sensation in newborns. Further, topically applied products containing ethanol alcohol may cause percutaneous toxicity in the newborn. Procurers should ask the product supplier/manufacturer to provide a list of inactive ingredients to ascertain that the product contains no alcohol.

Packaging and labeling

As sunlight adversely affects the stability of chlorhexidine digluconate, transparent primary containers should be avoided.Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Additional information about the storage requirements can be found in the "Storage, Stability and Degradation" section.

Name of the Medicinal Product

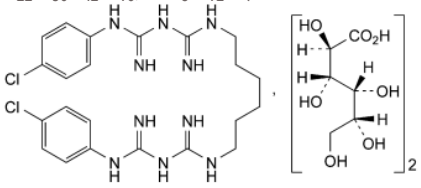
7.1% Chlorhexidine digluconate solution or gel for umbilical cord care

Chemical Name

Chlorhexidine digluconate;
1,1'-(hexamethylene)bis[5-(4-chlorophenyl)biguanide] di-d-gluconate, 1,1'-(hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide] di-d-gluconate

Chemical Structure

$C_{34}H_{54}C_{l2}N_{10}O_{14}$
$C_{22}H_{30}C_{l2}N_{10}$, $2C_6H_{12}O_7$



Pharmaceutical Form

Topical solution—clear, colorless or pale yellow liquid
Topical gel—colorless to yellow translucent gel

Qualitative and Quantitative Composition

Solution
Chlorhexidine digluconate topical solution is a solution of "chlorhexidine digluconate solution" in a suitable vehicle. It contains chlorhexidine digluconate 7.1% (equivalent to 4% chlorhexidine).

Each 100 mL contains 7.1 g chlorhexidine digluconate equivalent to 4 g chlorhexidine.

List of excipients:
– Purified water
– Sodium hydroxide
– Benzalkonium chloride (optional)

Gel
– Chlorhexidine digluconate topical gel is a solution of chlorhexidine digluconate in a suitable water-miscible basis. It contains chlorhexidine digluconate 7.1% (equivalent to 4% chlorhexidine).
– Each sachet contains a 3-g dose containing 213 mg of chlorhexidine digluconate equivalent to 120 mg chlorhexidine.

Composition[3]:

COMPONENT	QUANTITY (% W/W)
Chlorhexidine digluconate solution, 20% w/v	37.81*
Guar gum	1.40
Sodium acetate trihydrate	0.10
Purified water	QS to 100

** It may be adjusted for potency.*

Packaging and Presentation

The WHO EMLc includes two presentations for umbilical cord care: 7.1% chlorhexidine digluconate solution or gel, delivering 4% chlorhexidine.

The 7.1% chlorhexidine digluconate solution is packaged in nozzle/dropper plastic bottle.

The 7.1% chlorhexidine digluconate gel is packaged in foil laminate sachet or aluminum tube.

[3] Based on the formulation of an innovator product, Umbipro® developed by GSK available at https://www.usp-pqm.org/sites/default/files/pqms/article/gsk-chx-gel-tech-transfer-report-6-20-2019.pdf

SUPPLY

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

WHO-prequalified products

7.1% chlorhexidine digluconate for umbilical cord care is not included in the WHO PQP. Therefore, no WHO-prequalified products are available.

SRA-approved products

As of June 2022, there are no SRA-approved products for 7.1% chlorhexidine digluconate for umbilical cord care. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has provided a positive opinion for Umbipro® for the prevention of omphalitis (infection of the umbilical cord) in newborn infants. This application was submitted and reviewed under Article 58 of Regulation (EC) No. 726/2004, a pathway offered by EMA in cooperation with WHO for products exclusively intended for markets outside the European Union. However, this medicine product is no longer authorized[4].

The 7.1% chlorhexidine digluconate for umbilical cord care product has been developed to be used in low resource-settings where the burden of disease is high. Therefore, the product has no regulatory approval from SRAs because it is not intended for use in high-resource settings. It should be noted that there may be other chlorhexidine products approved by the SRAs, but they may be presented in different dosage forms and/or concentrations that are not indicated for umbilical cord care.

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

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

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

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk /

[4] https://www.ema.europa.eu/en/documents/outside-eu-summary/umbipro-medicine-overview_en.pdf

- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic:
- https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects manufacturers among GMP approved manufacturers via tenders (UNICEF contract awards) to supply products usually over a two- or three-year period.[5] The recent lists (from 2020) did not include 7.1% Chlorhexidine digluconate solution or gel.

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

Related products

Other formulations of chlorhexidine that exist in the market include:

- Topical solution (liquid, cloth, sponge applicators, swab sticks) available at concentrations 2%, 3.15%, 4%, and 5% of chlorhexidine gluconate/digluconate with and without isopropyl alcohol. Used for skin preparation for surgery, invasive procedures, and central lines to prevent hospital-acquired infections.
- Scrub solution (liquid detergent) available at concentrations 2% and 4% of chlorhexidine gluconate/digluconate with isopropyl alcohol. Used for preoperative bathing, general skin cleansing to prevent hospital-acquired infection, and preoperative hand scrub and hand disinfection to prevent the spread of microorganisms.
- Irrigation solution (chlorhexidine and cetrimide) available at concentrations 2% and 4% of chlorhexidine gluconate/digluconate. Used for irrigation of wounds to prevent infection.
- Topical cream (chlorhexidine and cetrimide) available at concentrations 0.1% of chlorhexidine gluconate/digluconate with cetostearyl alcohol. Used for wound cleaning (over-the-counter first-aid cream) to prevent infection.
- Washcloth available at concentration 2% of chlorhexidine gluconate/digluconate. Used for daily bathing in intensive care unit (ICU) patients to prevent hospital-acquired infection.
- Gauze dressing available at concentration 0.5% of chlorhexidine acetate. Used for wound or burn dressing to prevent infection.
- Catheter dressing (gel pad, foam disk, semipermeable transparent dressing) available at concentration 2% of chlorhexidine gluconate/digluconate. Used for catheter dressings to prevent hospital-acquired infection.
- 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.

[5] Available at https://www.unicef.org/supply/contract-awards

- Dental solution (oral rinse or spray) at concentrations 0.12% and 0.2% of chlorhexidine gluconate/digluconate with ethanol. Used to decontaminate oral cavity to prevent ventilator-associated pneumonia and for periodontal disease and mucositis treatment.
- Concentrated stock solution available at concentration 20% of chlorhexidine gluconate/digluconate. Used for preparation of dilutions for skin cleansing and general disinfection.

It is important to note that the WHO EMLc recommends only chlorhexidine 7.1% (digluconate) delivering 4% chlorhexidine solution or gel for topical application umbilical cord care to prevent cord infection and/or sepsis and reduce neonatal mortality. Therefore, it is recommended that the procurement agency must focus on procurement of the presentations as per the WHO EMLc.

STORAGE, STABILITY, AND DEGRADATION

7.1% chlorhexidine digluconate solution and gel forms are stable at room temperature and do not require cold chain storage.

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

Storage condition: Store below 30˚C and away from direct sunlight.

The active substance, chlorhexidine digluconate, degrades (unavoidably) via hydrolysis with multiple degradation pathways and generates a range of impurities, notably 4-chloroaniline (4-CA), which has been shown to be genotoxic and carcinogenic in non-clinical studies. The 4-CA impurity (Impurity P in the Ph.Eur. specifications for chlorhexidine digluconate solution) is known to increase with time and temperature and to be impacted by pH. The content of 4-CA in the finished product can be minimized by the following measures: controlling pH and 4-CA level in the input active substance; selection of excipients that minimize formation of 4-CA; providing instructions on appropriate storage conditions; and testing the finished product quality against specifications for a specific pH range and 4-CA content.

The active substance stability is optimal between pH 5.5 and 7.0. The pH of the active substance is important to the rate of 4-CA formation, with the primary degradation mechanisms being direct formation of 4-CA from chlorhexidine under acidic conditions and indirect 4-CA formation under alkaline conditions. To minimize levels of 4-CA and other drug-related impurities in the finished product, the pH of the input chlorhexidine digluconate active substance should be controlled as per Ph.Eur. requirements, i.e. pH 5.5–7.0.

PRODUCT SPECIFICATIONS

7.1% chlorhexidine digluconate topical solution form must meet pharmacopeial specifications,[6] such as those of the International Pharmacopeia and USP, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The

[6] *Chlorhexidine digluconate* is used in the International Pharmacopeia, while *chlorhexidine gluconate* is used in the British and US Pharmacopeias.

testing parameters and acceptance criteria of the two pharmacopeias are similar, except the pH limits are slightly different.

7.1% chlorhexidine digluconate topical gel form must meet pharmacopoeial specifications, such as those of the British and US Pharmacopoeias, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Table CD-2. International Pharmacopeia Specifications for Chlorhexidine Digluconate Topical Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) TLC	The principal spot obtained with solution (a) corresponds in position, appearance and intensity to that obtained with solution (b).	1.14.1 Thin-layer chromatography
b) Spectro-photometry	The absorption spectrum of the resulting solution, when observed between 200 nm and 320 nm, exhibits two maxima at about 231 nm and 255 nm, and two minima at about 218 nm and 242 nm.	1.6 Spectrophotometry in the visible and ultraviolet regions
c) HPLC	The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to chlorhexidine in the chromatogram obtained with solution (2).	1.14.4 High-performance liquid chromatography
pH	5.0–7.5	1.13 pH value
Assay	90.0–110.0%	1.14.4 High-performance liquid chromatography
Impurity P (4-chloroaniline)	In the chromatogram obtained with solution, (1) the area of any peak corresponding to 4-chloroaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.05% [m/m] of 4-chloroanilin in the amount of chlorhexidine digluconate solution used to prepare the topical solution).	1.14.4 High-performance liquid chromatography

Table CD-3. US Pharmacopeia Specifications for Chlorhexidine Digluconate Topical Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) HPLC	The retention time of the major peak for chlorhexidine from the sample solution corresponds to that of the standard solution, as obtained in the assay.	USP<621>
b) TLC	The principal spot from the Sample solution corresponds in color, size, and Rf value to that from the standard solution.	USP<201>
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. US Pharmacopeia Specifications for Chlorhexidine Digluconate Topical Gel

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) UV	The UV absorption spectrum of the sample solution exhibits two maxima at 231 and 255 nm and two minima at 222 and 242 nm.	USP<197U>
b) HPLC	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay.	USP<621>
c) TLC	The principal spot of the sample solution corresponds in color, size, and Rf value to that of the standard solution.	USP<201>
pH	5.0–7.0	USP<791>
Assay	90.0–110.0%	USP<621>
Impurities (p-chloroaniline)	NMT 0.35%	USP<621>

Additional tests

Solution: Minimum fill and microbial limits should be included in the product specification.

Gel: Apparent viscosity, minimum fill, and microbial limits should be included in the product specification.

For gel packaged in sachets, the seal integrity test should be considered as in-process control.

7.1% CHLORHEXIDINE DIGLUCONATE ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

7.1% Chlorhexidine digluconate solution or gel (delivering 4% chlorhexidine) is indicated for prophylaxis of omphalitis (infection of the umbilical cord) in newborn infants.

Posology, method, and duration of administration

Posology

The recommended dose is a 3-g sachet applied once daily for 7 days. Health care providers should take account of local umbilical cord care guidelines regarding single-dose application. The first application must occur within 24 hours of birth.

For infants born at less than 32 weeks' gestation (or weighing less than 1,500 g at birth), the recommended dose is a single 3-g sachet applied once only in the first 24 hours after birth (see "Special warnings and precautions for use" section).

Method of Administration

Apply 7.1% chlorhexidine digluconate solution or gel as soon as possible within 24 hours after birth. Clean the umbilical cord stump and the skin around the base of the stump with a dry cloth prior to applying 7.1% chlorhexidine digluconate solution or gel. Apply adequate content of the sachet to ensure complete coverage of the umbilical cord, from the cut surface to the base and including the immediate surrounding abdominal skin. Wash hands before and after use.

7.1% chlorhexidine digluconate solution or gel should not be applied in combination with any other product. Occlusive dressings should not be applied to the umbilical cord stump, as doing so could increase the absorption of the product through the dermis.

Contraindications

This product should not be handled by anyone with a known history of hypersensitivity to chlorhexidine or to any of the excipients in this formulation.

Special warnings and precautions for use

For external use only. Do not inject or swallow.

Keep out of the eyes and ears and do not use over large areas of the body. If the product comes into contact with the eyes, wash out promptly and thoroughly with clean water.

There have been reports of hypersensitivity and skin irritation after topical administration of chlorhexidine, including generalized allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is not known, but available literature suggests this is likely to be very

rare. Use of the product should be discontinued and immediate medical help should be sought in case of any symptoms that may indicate an allergic reaction.

If skin irritation or redness occurs, prompt medical advice should be sought.

Treatment with chlorhexidine topical solution or gel may be associated with the development of methemoglobinemia, via degradation to 4–chloroaniline, although this has not been observed in clinical trials. This risk is likely to be increased in infants born prematurely, specifically at less than 32 weeks' gestation or weighing less than 1,500 g at birth. The treatment should be discontinued if symptoms and signs associated with methemoglobinemia, such as cyanosis or breathlessness, are observed and immediate medical advice sought.

The use of chlorhexidine solutions, both alcohol-based and aqueous, for skin antisepsis prior to invasive procedures has been associated with chemical burns in neonates. Based on available case reports and the published literature, this risk of chemical burns appears to be higher in preterm infants, especially those born before 32 weeks' gestation, and occurs within the first 2 weeks of life.

Interaction with other medicinal products and other forms of interaction

None known.

Pregnancy and lactation

Not intended for this patient population.

Effects on ability to drive and use machines

Not relevant.

Undesirable effects

Adverse reactions

Adverse reactions are classified by system organ class. Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented below.

Frequencies were defined as follows: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

The adverse reactions shown below have been associated with post-marketing data from different marketed chlorhexidine formulations (antiseptic solution, antiseptic cream, and antiseptic mouthwash). No post-marketing data are available for the 7.1% gel formulation.

Immune system disorders

- Hypersensitivity and anaphylaxis: frequency not known.

Skin and subcutaneous tissue disorders:

- Allergic skin reactions such as erythema and skin irritation: frequency not known.

Description of selected adverse reactions

The most serious reported adverse reactions to medicinal products or devices containing chlorhexidine are systemic hypersensitivity/anaphylaxis; see "Special warnings and precautions for use" section. Signs of a hypersensitivity reaction include rash, urticaria, angioedema, difficulty breathing, collapse, or loss of consciousness.

Overdose

This has not been reported.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of chlorhexidine products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on chlorhexidine digluconate solution or gel for umbilical cord care.

API

The API for 7.1% chlorhexidine digluconate solution or gel for umbilical cord care is 20% chlorhexidine digluconate solution.

Chlorhexidine digluconate solution (API) is not included in the WHO PQP. Therefore, no WHO-prequalified chlorhexidine digluconate solution exists.

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

Table CD-5. Manufacturers of Chlorhexidene Digluconate Solution API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Chlorhexidine digluconate solution (monograph number 658)	Medichem, S.A. Sant Joan Despí, Spain	R1-CEP 1993-009-Rev 04	2/16/2009	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	R.N. Laboratories Mumbai, India	R1-CEP 2006-171-Rev 02	05/17/2018	Chemistry
Chlorhexidine digluconate solution CDG (monograph number 658)	Medichem, S.A. Sant Joan Despí, Spain	R0-CEP 2017-128-Rev 01	12/20/2018	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Bajaj Healthcare Limited Thane (West), India	R0-CEP 2017-074-Rev 00	6/28/2019	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Evonik Operations GMBH Essen, Germany	R1-CEP 2001-343-Rev 05	8/31/2020	Chemistry
Chlorhexidine digluconate solution (monograph number 658)	Xttrium Laboratories, INC. Mount Prospect, USA	R0-CEP 2020-179-Rev 00	11/10/2021	Chemistry

Other manufacturers of chlorhexidine digluconate solution should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

Chlorhexidine digluconate solution must meet pharmacopeia specifications,[2] such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Note: 4-chloroaniline (4CA) has been shown to be genotoxic and carcinogenic in nonclinical studies. Therefore, it is suggested to procure API with the lowest 4CA levels.[3]

Excipients

The typical excipients of 7.1% chlorhexidine digluconate solution or gel for umbilical cord care are as follows. There are no special concerns regarding the excipients.

Table CD-6. Excipients of 7.1% Chlorhexidine Digluconate Solution or Gel

INGREDIENT	FUNCTION
Purified water	Vehicle
Sodium acetate trihydrate	pH enhancer
Sodium hydroxide	pH adjustment
Guar gum	Thickening agent—viscosity enhancer (used for the gel formulation)
Benzalkonium chloride	Preservative (optional)

Note: sodium hydroxide could lead to the formation of turbid solution and decrease the chemical stability of the drug product in reference to 4CA and total impurities content. 0.1% w/w sodium acetate trihydrate is a suitable alternative to adjust the pH, providing better stability with respect to 4CA content.[9]

The quality of excipients should be compliant with recognized pharmacopeias (Ph.Int., Ph.Eur./BP, or USP).

Sodium acetate trihydrate is used as the pH stabilizer in the innovator product, as it was shown to result in the lowest level of drug-related impurities.[4] The use of buffer salts for maintaining the pH of the solution should be restricted due to the incompatibility of chlorhexidine gluconate with other anionic materials such as borates, phosphates, acetates, nitrates, and chlorides.

For the gel formulation, guar gum is an economical thickener and stabilizer for producing the gel form. The very high viscosity attained at low concentrations makes guar gum an excellent thickener. The other advantage of guar gum is that it is non-ionic, so it is stable over a wide pH range.

The source of guar gum may impact active substance stability. The guar gum may contain acidic impurities as a carryover from the extraction/purification process, potentially causing the

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.
[2] Chlorhexidine digluconate is used in the International and European Pharmacopeias, while chlorhexidine gluconate is used in the US Pharmacopeia
[3] PQM. GSK Chlorhexidine Digluconate (7.1%) Gel Technology Transfer Report. 2018. U.S. Pharmacopeial Convention. The Promoting the Quality of Medicines Program. Rockville, Maryland.
[4] EMA assessment report of Umbipro®.

degradation of chlorhexidine. Studies using guar gum from different suppliers are recommended as part of the finished product development.

Some formulations may contain benzalkonium chloride as a preservative. However, a study by PATH[5] indicated that benzalkonium chloride did not offer added value as a preservative, since it was not imparting additional stability to the chlorhexidine formulation. Since the concentration of chlorhexidine in the formulation is very high (4%), chlorhexidine will probably kill any bacteria with or without benzalkonium chloride, thereby making the role of benzalkonium chloride indistinguishable.

It should be noted that when benzalkonium chloride is used in the formulation, a light brown coloration of the solution can be observed, due to the interaction of chlorhexidine with chloride from benzalkonium chloride. The discoloration does not adversely affect the potency of chlorhexidine. Product specifications may need to be changed to accommodate the appearance characteristics of the chlorhexidine digluconate solution or gel if used in combination with benzalkonium chloride.

Manufacturing process

Both chlorhexidine digluconate solution and gel are straightforward products to manufacture, involving a standard manufacturing process.

Solution and gel form have very similar manufacturing processes, with the only difference being in the step where guar gum is added to thicken the product into a gel.

For solution form, the typical manufacturing process involves preparing chlorhexidine digluconate solution in water, followed by pH adjustment and filling into bottles.

For gel form, the typical manufacturing process involves dissolving sodium acetate trihydrate in water, followed by dispersion and hydration of guar gum. The solution is heated at this stage to aid hydration of the guar gum. The resultant gel is then cooled, before addition and mixing of chlorhexidine digluconate solution. The gel is subsequently de-aerated using vacuum and then discharged into a holding vessel prior to being filled into aluminum tube or foil laminate sachets using suitable form-fill-seal packaging equipment.

Large-scale production of the gel formulation containing guar gum requires specialized equipment (high-pressure homogenizer). High-pressure homogenization is essential to the quality and stability of the gel formulation since this is a very effective way to create homogeneity in the gel texture while at the same time producing a very stable product, compared to the traditional devices such as agitators, stirrers, rotor-stator devices, or colloid mills. The result is a homogeneous, effective product with superior stability and shelf life.

Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture. When adding/dispersing the guar gum, the gel temperature and high-shear mixing time should be well defined. The gel should be cooled before the addition of chlorhexidine digluconate solution.

Packaging

The primary package material must comply with USP, Ph.Eur., and/or European Community requirements. Since sunlight adversely affects the stability of chlorhexidine digluconate, transparent primary containers should be avoided.

[5] PATH. 2010. “Stability Data of Chlorhexidine Formulations: PATH Summary.” PATH: Seattle.

Notes:

- *The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[6, 7]

Solution

The 7.1% chlorhexidine digluconate solution is packaged in an HDPE bottle with polypropylene screw closure.

The nozzle/dropper bottles provide the best product coverage on the umbilical stump. The nozzle minimizes occasions in which users directly contact the umbilical cord. However, depending upon the country, users may associate the small (single-day) application size nozzle/dropper bottles with newborn eye or ear drops. Therefore, clear instructions should be put on the product label.

Spray bottles work only in the upright position and might make it difficult for users to achieve complete coverage of the cord stump. Wide-mouth bottles may increase the risk of product contamination and spillage.

Gel

The 7.1% chlorhexidine digluconate gel is packaged in a foil laminate sachet or aluminum tube.

Aluminum tubes are commonly used for semi-solid pharmaceuticals. However, depending upon the country, users may associate the small (single-day) application size tubes with newborn eye ointment. Therefore, clear instructions should be put on the product label.

Sachets could be a lower-cost option. However, depending on the country, sachets might not be commonly used for pharmaceuticals; therefore, manufacturers might not have the appropriate equipment, and users might associate sachets with cosmetics rather than medicines, leading to confusion.

Note: The risk assessment for potential presence of leachables from the container closure system and from the manufacturing process should be carried out.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when pharmaceutically equivalent products are topical products prepared as aqueous solutions and contain the same API in the same molar concentration and the same excipients in similar concentrations as in the comparator product.

Umbipro®, the original product developed GlaxoSmithKline is not available in SRA countries. However, in collaboration with the U.S. Pharmacopeial Convention (USP) Promoting the Quality of

[6] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[7] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

Medicines (PQM) Program, GlaxoSmithKline has provided a Technology Transfer Report[8] that is available in the public domain. This document addresses the development of the formulation, analytical testing, key information for the manufacturing and primary packaging processes, and describes Clinical and Nonclinical Studies references. In addition, the PQM has also issued a report describing technical information to support the dossier preparation[9]. In the absence of a comparator product available in SRA countries, both guidelines are suitable references to support the chlorhexidine digluconate 7.1% gel product development and submission.

[8] PQM. GSK Chlorhexidine Digluconate (7.1%) Gel Technology Transfer Report. 2018. U.S. Pharmacopeial Convention. The Promoting the Quality of Medicines Program. Rockville, Maryland.
[9] PQM+. 2020. Chlorhexidine digluconate (7.1%) Gel Dossier Aid. Submitted to the U.S. Agency for International Development by the PQM+ Program. Rockville, MD: U.S. Pharmacopeial Convention