STERILITY PAPER

HEXI PREP®

2% chlorhexidine digluconate in
70% isopropyl alcohol impregnated pad

The need for sterility for skin disinfection products relating to preparation of skin prior to a procedure that breaks the skin integrity.

from the makers of **clinell**®

STERILE

BACKGROUND

There are three principle applications of skin antiseptics in healthcare settings: to prepare the skin for an invasive procedure (e.g. before an injection or placement of a sterile intravascular device), to prepare the skin prior to surgery (e.g. washing on the morning of surgery), and to help to reduce skin colonisation by organisms that can cause infections in high-risk settings, for example critical care units where a large number of invasive devices are used, by daily bathing using chlorhexidine impregnated cloths.

- GAMA Healthcare produces HEXI PREP, a sterile single sachet pad containing chlorhexidine digluconate and isopropyl alcohol designed for skin preparation prior to invasive procedures.
- GAMA Healthcare also produce aqueous chlorhexidine impregnated wash cloths.

This paper summarises the regulatory position and the evidence of the need for sterility in products of this type.

REGULATORY POSITION

The Medicines and Healthcare products Regulatory Agency (MHRA) is an executive agency sponsored by the Department of Health and regulates medicines, medical devices and blood components for transfusion in the UK. The MHRA requirement is that:

- Where the skin is treated in advance of and not immediately prior to surgery (i.e. the night before or the morning of surgery), a non-sterile product is considered acceptable.
- With respect to skin antiseptics indicated for use immediately prior to invasive procedures, the MHRA considers that such drug products should be manufactured as sterile.
- MHRA is currently advising pharmaceutical companies that these solutions are manufactured as sterile when intended for use as a medicinal product.
- The Committee on Human Medicines (CHM) also advises that these products are manufactured sterile.
- Despite these recommendations, not all commercially available skin antiseptic and preparation products are manufactured sterile.

EVIDENCE OF THE NEED FOR STERILITY

- Although such products are bactericidal, they are not sporicidal. It is known that some solvents, such as the raw material isopropyl alcohol, can be contaminated with bacterial spores. Also, some Gram-negative bacteria are able to survive and even proliferate in some disinfectant and antiseptic solutions.[1]
  - Potential pathogens associated with the contamination of skin antiseptics include *Bacillus cereus, Burkholderia cepacia, Pseudomonas aeruginosa, and Serratia marcescens*.[2]
- Consequently there is a risk that non-sterile antiseptic solutions may be a source of infection, given their use. The likelihood may be low, however the consequences may be severe.
- A summary of incidents related to microbial contamination of topical skin antiseptic products was published in the New England Journal of Medicine in 2012.[2]
- Outbreaks including infections from contaminated antiseptic skin products include:
  - An outbreak of *Serratia marcescens* affecting 16 patients in Spain published in 2017 associated with bottles of chlorhexidine contaminated during manufacture.[3]
  - An outbreak of *Burkholderia lata* affecting 8 patients in 2 Australian hospitals published in 2016 linked to chlorhexidine mouthwash contaminated during manufacture.[4]
  - An outbreak of *Bacillus cereus* affecting 3 patients in the USA published in 2012 associated with contaminated alcohol skin preparation pads.[5]
  - Outbreak of *Burkholderia cepacia* due to contamination of chlorhexidine mouthwash in 2012.[6]
  - Outbreak of *Burkholderia cepacia* complex due to contamination of chlorhexidine solution in 2013.[7]
- Several product recalls have occurred related to contaminated skin antiseptic products, including:
  - Chlorhexidine based skin preparation due to fungal contamination in 2020.
  - Oral chlorhexidine rinse due to *Burkholderia sp.* in 2020.
  - Chlorhexidine-impregnated washcloths due to *Burkholderia* sp. contamination in 2016.
  - Alcohol wipes due to bacterial contamination in 2011.

Further examples and discussion from the USA perspective was also published in Infection Control Today[8] particularly highlighting difficulties in the process of sterilising these products.

SUMMARY

Due to the risk of contamination of skin antiseptic products during the manufacturing process, MHRA in the UK recommend that all skin antiseptic products for medicinal use are manufactured sterile. Whilst this is beyond regulatory requirements in some countries, it will maximise patient safety and reduce the risk of product recalls, which are expensive and disruptive for consumers and product providers.

Prescribing information: HEXI PREP 2% w/v / 70% v/v for cutaneous use. Refer to Summary of Product Characteristics before prescribing. **Presentation:** Each impregnated pad contains 1.5 ml or 3.0 ml of 20 mg chlorhexidine digluconate and 0.7 ml of isopropyl alcohol. **Indication:** Disinfection of the skin prior to invasive medical procedures that do not require a clean air environment. **Dosage & administration:** There are two pad sizes available. HEXI PREP may be used on all age groups and patient populations. Use with care in newborn babies, especially those born prematurely. The choice of pad size will depend on the size of the area to be disinfected, the invasive procedure and the clinician's preference. For both non-sterile and sterile procedures, the user should wear gloves during application. Keep the pad folded and press firmly against the skin on the intended area and wipe back and forth for a total of 30 seconds. Allow to air dry completely. It is recommended that HEXI PREP solution remains on the skin post-procedure to provide continued antimicrobial activity. If removal is necessary, remove with soap and water or alcohol. **Contraindications:** The medicinal product is contraindicated where patients have shown previous hypersensitivity to chlorhexidine or isopropyl alcohol. **Warnings & precautions:** The solution is flammable. Do not use with electrocautery procedures or other ignition sources until dry. Remove any soaked materials, drapes or gowns before proceeding with the intervention. Do not allow the solution to pool in skin folds or under the patient or drip onto sheets or other material in direct contact with the patient. Where occlusive dressings are to be applied to areas previously exposed to HEXI PREP, care must be taken to ensure no excess product is present prior to application of the dressing. For external use only on intact skin. Do not use on open skin wounds. Avoid prolonged contact with the skin. Do not use on broken or damaged skin. Avoid contact with neural tissue, the middle ear, the eyes and mucous membranes. Chlorhexidine-containing products are known causes of anaphylactic reactions during anaesthesia. The symptoms of anaphylactic reactions might be masked in an anaesthetised patient. If symptoms of an anaphylactic reaction are detected during anaesthesia, chlorhexidine-related allergic reactions should be considered. When chlorhexidine-related reaction during anaesthesia is suspected, other products containing chlorhexidine used during anaesthesia (e.g. IV lines) should be removed. Special precaution should be taken to avoid patient exposure to any other product containing chlorhexidine during the course of the treatment. The use of chlorhexidine solutions, both alcohol based and aqueous, for skin antisepsis prior to invasive medical procedures has been associated with chemical burns in neonates. Based on available case reports and the published literature, this risk appears to be higher in preterm infants, especially those born before 32 weeks of gestation and within the first 2 weeks of life. **Pregnancy & lactation:** There are no studies with this product in pregnant or lactating women. No effects during pregnancy are anticipated since systemic exposure to chlorhexidine digluconate is negligible. HEXI PREP can be used during pregnancy. No effects on the breastfed newborn infant are anticipated since the systemic exposure of breast-feeding women to chlorhexidine digluconate is negligible. HEXI PREP can be used during lactation. **Undesirable effects:** Skin disorders: very rare allergic or irritation skin reactions have been reported with chlorhexidine and isopropylalcohol: erythema, rash (e.g. erythematous, papular, or maculopapular), pruritus and blisters or application site vesicles. Other local symptoms have included skin burning sensation, pain and inflammation. Frequency not known: dermatitis, eczema, urticaria, chemical burns in neonates. Immune disorders: Frequency unknown: Hypersensitivity including anaphylactic shock. Cases of anaphylactic reactions have been reported during anaethesia. Common reported reactions: associated with site reactions often within the area of application and very rarely spread. This product may cause a severe allergic reaction. Symptoms may include wheezing / difficulty breathing, shock, facial swelling, hives or rash. Use of HEXI PREP is contraindicated where patients have shown previous hypersensitivity to chlorhexidine or isopropyl alcohol. If hypersensitivity or an allergic reaction occurs, stop use and seek medical help right away. **Reporting adverse events:** Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GAMA Healthcare Ltd. **Per pad costs** (NHS Supply Chain; ex VAT): HEXI PREP(CHEX15) 1.5 ml UK £0.28, HEXI PREP (CHEX30) 3.0 ml UK £0.66. **Legal category:** UK GSL. **Marketing Authorisation Numbers:** HEXI PREP (PL 40867/0002). **Marketing Authorisation Holder:** GAMA Healthcare Ltd., Maylands Building, Maylands Avenue, Hemel Hempstead Industrial Estate, Hemel Hempstead, Hertfordshire, HP2 7TG. **Date of issue:** May 2023.

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GAMA Healthcare Ltd., The Maylands Building, Maylands Avenue,
Hemel Hempstead, Hertfordshire, HP2 7TG, UK.
+44 (0)20 7993 0030 | info@gamahealthcare.com | www.gamahealthcare.com

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