CBG MEB

Public Assessment Report

Scientific discussion

Chloorhexidinetinctuur Fresenius Kabi, cutaneous solution 5 mg/ml /70% v/v

Chloorhexidinetinctuur Fresenius Kabi, rood, cutaneous solution 5 mg/ml /70% v/v

(chlorhexidine digluconate/ethanol)

NL License RVG: 117750, 117752

Date: 14 February 2018

This module reflects the scientific discussion for the approval of Chloorhexidine-tinctuur Fresenius Kabi and Chloorhexidinetinctuur Fresenius Kabi rood. The marketing authorisation was granted on 29 November 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
FNA	Formularium der Nederlandse Apothekers (*Dutch Pharmacists Formulary*)
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
RH	Relative Humidity
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (*National Institute for Public Health and the Environment*)
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
WIP	Working party on infection prevention

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Chloorhexidinetinctuur Fresenius Kabi and Chloorhexidinetinctuur Fresenius Kabi, rood, cutaneous solution 5 mg/ml /70% v/v, from Fresenius Kabi Nederland BV.

The product is indicated for:

- hygienic and preoperative hand disinfection
- disinfection of the intact skin prior to invasive medical procedures.

A comprehensive description of the indications and posology is given in the SmPC.

The product contains two well known active substances: ethanol and chlorhexidine digluconate solution. As a disinfectant, ethanol works by denaturing proteins and dissolving lipids. It is ineffective against spores. Ethanol is typically used in concentrations of 70 percent, because higher concentrations evaporate too quickly and lower concentrations are not as effective.
Chlorhexidine is a cationic poly biguanide. Its antimicrobial action is due to a disruption of the cell membrane through non-specific interaction with acidic phospholipids of the cell membranes. It has a bactericidal or bacteriostatic action against a wide range of gram-positive and gram-negative bacteria. It is relatively ineffective against mycobacteria. It is practically not viricidal although it inhibits some viruses and is active against some fungi. Its activity against Hepatitis B virus has not been established. Most of the currently used chlorhexidine formulations are based on the gluconate salt. The benefits of combining the two active substances include the immediate reduction of bacterial density by alcohols and the prolonged antibacterial effect of chlorhexidine.

This application concerns a bibliographical application based on well-established medicinal use of chlorhexidine gluconate 0.5% and ethanol 70% v/v cutaneous solution. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The present product formulation has been included in the Dutch Pharmacists Formulary (*Formularium der Nederlandse Apothekers* (FNA)) for decades. Marketing authorisations have been granted in the Netherlands for a number of medicinal products with a similar composition. These include ChloraPrep 2% w/v/70% v/v cutaneous solution (chlorhexidine gluconate 20 mg/ml and isopropyl alcohol 0.70 ml/ml; NL License RVG 110531) and Hibisol, cutaneous solution (chlorhexidine gluconate 5 mg/ml and isopropyl alcohol 600 mg/ml; NL License RVG 09312). Hibisol also contains the non-active constituents cyclomethicone 5 and isopropyl isostearate.

II. QUALITY ASPECTS

II.1 Introduction

Chloorhexidinetinctuur Fresenius Kabi contains 5 mg/ml chlorhexidine digluconate and 0.70 ml/ml ethanol. It is a clear, colourless solution or a clear, orange to orange red solution.
The coloured solution has a staining effect, and indicates whether the skin area prepared has been fully covered.

The product is contained in white opaque HDPE bottles with a PE cap: 125 ml, 250 ml and 1000 ml; white opaque HDPE bottles with PP cap: 1000 ml.

The formulations contain water for injections as an excipient, and the coloured solution also contains the colourant phenol red (phenolsulfonphthalein).

II.2 Drug Substances

The active substances chlorhexidine digluconate solution (20% w/v) and ethanol anhydrous both are well established active substances described in the European Pharmacopoeia (Ph.Eur.). Chlorhexidine digluconate is an almost colourless or pale-yellowish liquid. Ethanol anhydrous is a colourless, clear, volatile, flammable liquid. The active substances are miscible with water.

For chlorhexidine digluconate solution the CEP procedure is followed. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
For chlorhexidine digluconate a CEP has been submitted; therefore no details on the manufacturing process have been included.
Ethanol is manufactured from ethylene and water. Both substances are combined in a vapour phase reaction which takes place at high pressure and temperature over an acid catalyst. Ethanol is extracted by passing through a 2 stage separation removing any unreacted ethylene which is returned to the reactor loop. The crude ethanol from this gas separation is purified within the distillation section and dried by molecular sieve to produce the final product. Since the manufacturing process is a continuous process no validation of full scaled batches is possible. Batch analytical data have been provided for 10 batches. All batches comply with the specification, the results are comparable.

Quality control of drug substances
The chlorhexidine digluconate solution (20%) drug substance specification complies with the requirements of Ph. Eur., with appropriate additional tests.
The specification of ethanol anhydrous is according to the Ph.Eur. with additional methods for water content and chlorides. The specifications are acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three production scaled batches per drug substance.

Stability of drug substances
Chlorhexidine digluconate solution is stable for 2 or 3 years, depending on the container, at a temperature not exceeding 25°C. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
Ethanol anhydrous is fully tested to ensure compliance with its specification immediately prior to its use in the manufacture of the product.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development has been adequately described. The formulation is well known, and the manufacturing process is straightforward. The provided information on density, pH and microbiological control is sufficient. Microbiological contamination of the finished product is tested according to Ph.Eur. 2.6.12. With respect to microbiological validation of the moulding process of the bottles the temperature and pressure assure that an acceptable sterility assurance level is obtained. The pH is approximately 7.5 to 8. This is also an optimal pH from a chemical point of view as aqueous solutions in general are most stable at pH 5 to 8.
Comparable products registered in the Netherlands are Chloraprep 2% w/v /70% v/v and Chloraprep 2% w/v /70% v/v coloured cutaneous solution and Hibisol 5 mg/ml and 600 mg/ml cutaneous solution.
Although both products use isopropyl alcohol instead of anhydrous ethanol, isopropyl alcohol is similar in function to ethanol. It evaporates at a similar rate and destroys bacterial and viral cells by the same mechanism. Hence, from chemical-pharmaceutical point of view this difference is not expected to result in different properties compared to already approved products.

Manufacturing process
The manufacturing process consists of the following steps: mixing of the ingredients, moulding of the HDPE bottles, aseptic filling and closing of the bottles. The formulations have been produced for many years for the Swedish and Norwegian market. Given the nature of the product, the simplicity of the manufacturing process and the experience of the drug product manufacturer the process can be designated as a standard process.
The manufacturing process with respect to filling and packaging of the drug product has been adequately validated. Process validation data for homogeneity of the product has been presented for 26 full scaled batches in the different bottle sizes.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of chlorhexidine, gluconate, ethanol and phenol red (coloured presentation only), assay of chlorhexidine digluconate, assay of ethanol, related substances and microbiological test.
The release and shelf-life requirements are identical except for the assay of chlorhexidine digluconate. The specification is acceptable.
Batch analytical data from the proposed production site have been provided on 3 production scaled batches of the colourless solution and 3 production scaled batches of the coloured solution, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 24 full scaled batches stored at 25°C/60% RH (up to 36 months) and 40°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the 125 ml, 250 ml or 1000 ml HDPE bottles.
For the colourless solution at long term (36 months time point) out-of-specification results were observed. For the coloured solution all results remained within specification. A photostability study was performed and no trends were observed.
Overall, based on the provided stability data a shelf life of 24 months, when stored below 25°C, has been granted.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Chloorhexidinetinctuur Fresenius Kabi and Chloorhexidinetinctuur Fresenius Kabi, rood, cutaneous solution 5 mg/ml /70% v/v have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Chlorhexidine is a cationic biguanide. Its antimicrobial action is due to a disruption of the cell membrane and the precipitation of cell contents. It has a bactericidal or bacteriostatic action against a wide range of gram-positive and gram-negative bacteria. It is relatively ineffective against mycobacteria. It is practically not viricidal although it inhibits some viruses and is active against some fungi. According to the Principles and Practice of Disinfection Preservation & Sterilization by Russell, Hugo & Ayliffe (2004[1]), concentrations of chlorhexidine 8 – 60 µg/ml induce a 99.99% kill of

[1] Russell, Hugo & Ayliffe's / edited by Adam P. Fraise, Peter A. Lambert, Jean-Yves Maillard. Principles and practice of disinfection, preservation and sterilization — 4th ed., 2004: chapter 2).

Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa and Salmonella typhimurium.

Bloomfield et al (1991)[2] described the development of standard suspension test methods for disinfectants and antiseptics for adoption in Europe. The majority of products (including alcohol 70% and 0.45% chlorhexidine in 63% alcohol i.e. Hibisol) diluted in water of standard hardness showed satisfactory activity producing a 4.5-5 log reduction in viable count within 5 minutes against Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus faecium, Proteus mirabilis and Candida albicans in the absence and presence of 1% albumin. All the products, when diluted with distilled water, produced greater than 5 log reduction in 60 min.

The dossier contains also a study report in which determination of bactericidal and yeasticidal activity is described based on 13727:2013+Al and 13624:2013 (phase 2 - step 1) European standard testing for an almost identical product (Ethanol 70%, Chlorhexidine digluconate 0.5%, cetiol, i.e. glyceride 1% w/w). The results showed that this product can be qualified as bactericidal against P. aeruginosa ATCC: 15442, S. aureus ATCC 6538, E. coli K12 NCTC 10538 and E. hirae ATCC 10541 ("10 log reductions of 6 and higher) and yeasticidal against C. albicans ATCC 10231 (10 log reductions of more than 6) under simulated clean (0.3 g/l BSA) conditions using a contact time of 30 s at 20°C (hygienic handrub) or 90 s at 20°C (surgical handrub). The product used in the study is almost identical to the product applied for, the only addition is cetiol, i.e. glyceride 1% w/w.

Ethyl alcohol at a concentration of 60-70% is an effective antiseptic; 70% ethanol provides an immediate kill of transient and resident microorganisms on the stratum corneum and 0.5% chlorhexidine gluconate binds to the superficial cell layers of the epidermis and provides a residual, or persistent, antimicrobial property that prevents regrowth of microorganisms. Ethyl alcohol (70%) is rapidly bactericidal and fast acting broad spectrum antiseptic, but is not considered persistent. It is tuberculocidal, fungicidal and virucidal, but not sporicidal. Its mechanism of action appears to be denaturation of proteins.

III.2 Pharmacokinetics

Chlorhexidine is poorly absorbed after topical or oral application because it is strongly bound to the skin and mucosa. This has been confirmed in animal and human studies after oral administration of 14C-labelled chlorhexidine. Oral bioavailability in animal studies was estimated to be less than 1%. In humans no 14C-labelled chlorhexidine was detected in blood after oral and topical application. Likewise no chlorhexidine was detected in blood of human infants washed in a 4% chlorhexidine solution.

III.3 Toxicology

Chlorhexidine has a low acute toxicity in mice and rats exposed to oral doses of chlorhexidine. After parenteral administration the toxicity is higher (approx. 4 folds). Studies of chronic administration (via drinking water) to rats for up to 2 years revealed no substance-related effects on ophthalmoscopy, clinical chemistry or urine analysis values. There were no significant gross pathological findings. Histopathology revealed histiocytosis of the mesenteric lymph nodes. The effects were dose related and reversible. At 40 mg/Kg body weight there was increased mortality, dehydration, aggression, incontinence and staining of the fur. In 6 and 12 month studies in dogs more toxicities were observed especially in the liver. The No Observed Effect Level (NOEL) was 0.5 mg/Kg body weight per day. Rat and rabbit experiments did not reveal signs of teratogenicity. There is no unequivocal evidence of mutagenicity of chlorhexidine. There is no evidence of carcinogenicity of chlorhexidine in mice.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH provided a justification for the absence of an Environmental Risk Assessment. The application relates to well-established use of the active substances. Therefore, no potential risks to the environment, other than those already known, are expected. Hence, an ERA is not required.

[2] Bloomfield S F, Arthur M, Looney E, Begun K & Patel H . 1991. Comparative testing of disinfectant and antiseptic products using proposed European suspension test method. Letters in Applied Microbiology 13, 233-231

III.5 Discussion on the non-clinical aspects

For this well-established use application, a non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.
0.5% chlorhexidine in 70% ethanol is one of the disinfectants recommended for skin disinfection by the National Institute for Public Health and the Environment (RIVM, Cleaning, disinfection and sterilisation in public healthcare – standard methods, available at www.rivm.nl). Chloorhexidinetinctuur Fresenius Kabi 5 mg/ml/70% v/v can therefore be considered suitable for disinfection purposes.
Information regarding pharmacokinetics and toxicology in the non-clinical overview was limited. However, chlorhexidine is a well-known active compound and systemic bioavailability after topical administration is expected to be minimal. The MEB agreed that additional non-clinical data are not necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns a well-established use application, based on article Article 10(a). No clinical studies have been submitted to support this application. This is acceptable as the active substances of the medicinal product have been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. A clinical overview has been provided, which is based on scientific literature.

IV.2 Clinical efficacy

Overall, the reported results in the described published studies support the conclusion that 0.5% chlorhexidine in 70% ethanol is effective in the reduction of resident skin flora to at least similar extent as the tested contemporary disinfectants. The product is suitable for disinfection of the intact skin prior to invasive medical procedures.

In addition to old published data it is relevant to note that in Europe, the most commonly used methods to test hand antiseptics are those of the European Committee for Standardization (CEN). The most common methods for testing hygienic hand antiseptic agents are *EN 1499* and *EN 1500* and to test surgical hand preparation the methods described in *CEN prEN 12791* are relevant.
The dossier contains a study report in which results of tests according to EN 12791 (2005) for an almost identical product for *surgical hand disinfection* is described The results showed that this product is suitable for surgical hand disinfection in the following application: Rub as many volumes of 6 ml into the hands as is necessary to keep them wet for 1.5 min. These results are in line with the results of published on the effect of 0.5% chlorhexidine in 70% ethanol on resident flora of the skin; although the used methodology in the old published studies was not entirely similar to the more recent CEN methodology. This product is almost identical to the product of this application. The only addition is cetiol, i.e. glyceride 1% w/w. Cetiol is a naturally based light emollient for skin care applications, otherwise it is an inactive substance. It is related to cyclomethicon 5 in the registered product Hibisol.

IV.3 Clinical safety

Chlorhexidine has been used widely for decades in hospital and other clinical settings for hand and wound cleansing, and skin and mucosal antisepsis before surgery or other procedures that penetrate these barriers. Formulations of chlorhexidine such as aqueous and alcohol-based solutions, gels and powders all have been used topically on adult, infant and neonatal skin.

Reported side effects have been few. Generalized allergic reactions to chlorhexidine have been reported but are extremely rare. Contact dermatitis, urticaria, and anaphylaxis have occurred after repeated skin exposures to chlorhexidine. Irritative skin reactions can occasionally occur.
The side effects are categorised as follows under “Incidence not known”:

- Blistering, burning, itching, peeling, rash, redness, swelling, or other signs of irritation on the skin

- Photosensitivity
- Allergic reaction (including anaphylaxis), contact dermatitis

Neonates:
Poor skin integrity of extremely low birth weight neonates may render them susceptible to skin toxicities from chlorhexidine such as burns. These were generally reported in infants with birth weights of less than 1500 grams. This may necessitate its use with caution in this population.
The Pharmacovigilance Risk Assessment Committee (PRAC) recommended to include special information in the SmPCs concerning the observed chemical burns in neonates after the use of chlorhexidine solutions, both alcohol based and aqueous, for skin antisepsis prior to invasive procedures in neonates[3]. Accordingly, the recommendations of the PRAC are included in sections 4.4 and 4.8 of the SmPC.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Chloorhexidinetinctuur Fresenius Kabi and Chloorhexidinetinctuur Fresenius Kabi, rood.

- Summary table of safety concerns as approved in RMP

Important identified risks	Chemical burns in neonates
Important potential risks	None
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

Benefits
The use of disinfectant combination solutions containing chlorhexidine gluconate 0.5% and ethanol 70% v/v is described extensively in the literature. This combination has been included in the FNA for decades. It is also listed as a skin disinfectant in de guideline 'Cleaning, disinfection and sterilisation in public healthcare – standard methods, 2003' of the National Institute for Public Health and the Environment (RIVM) and in the guideline 'Disinfection of skin and mucous membranes – revision March 2013' of the Working party on infection prevention (WIP).

The combination of chlorhexidine gluconate 0.5% and ethanol 70% v/v is recommended for the disinfection of skin or mucous membranes in:

- punctures in patients with severely impaired immune system such as agranulocytosis
- punctures of sterile body cavities or organs
- blood culture collection
- insertion of drains or catheters
- surgical procedures.

However, the WIP considers disinfection of skin and mucosa prior to administration of fluids via intradermal, intramuscular or subcutaneous injection, or venepuncture in patients with a healthy immune system not necessary (based on the article of Lieffers and Mokkink, 2002[4]).

Risks
Local adverse events of the skin may occur and in rare cases generalised allergic reactions have been described. Particularly in neonates caution is required when applying chlorhexidine containing products. A warning is included in the SmPC.

[3] http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2014/09/WC500174026.pdf
[4] M.A.M. Lieffers & H.G.A. Mokkink, *Desinfecteren van de huid vóór injecties niet van invloed op het ontstaan van infecties; een literatuurstudie,* Ned Tijdschr Geneeskd. 2002;146:765-7

Benefit/risk balance

The medicinal use of this disinfectant combination solution can be considered well-established. No specific composition has been laid down for this preparation in the FNA. The efficacy of Chloorhexidinetinctuur Fresenius Kabi as a disinfectant has been adequately described and is sufficiently justified based on scientific literature. The MEB considers the benefit/risk balance positive.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH has submitted a bridging report, referring to the successfully user tested PL for Chloraprep 2% w/v /70% v/v cutaneous solution. Both visual presentation and textual aspects of the two leaflets are very similar. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Chloorhexidinetinctuur Fresenius Kabi and Chloorhexidinetinctuur Fresenius Kabi, rood have a proven chemical-pharmaceutical quality. The use of the active substances is considered well-established for the approved indications: hygienic and preoperative hand disinfection, and disinfection of the intact skin prior to invasive medical procedures. The medicine has a favourable efficacy and safety profile. Adequate non-clinical and clinical literature data have been provided.

The Board followed the advice of the assessors.

The MEB considered that well-established use has been demonstrated for this medicinal product and has therefore granted a marketing authorisation. Chloorhexidinetinctuur Fresenius Kabi and Chloorhexidinetinctuur Fresenius Kabi, rood cutaneous solution 5 mg/ml /70% v/v were authorised in the Netherlands on 29 November 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse