ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Kenocidin Chlorhexidine digluconate 5 mg/ml, Teat dip solution for cattle (dairy)
(For all CMSs except Spain)

Kenocidin 5 mg/g, Teat dip solution for cattle (dairy) Chlorhexidine digluconate
(Spain)

PuAR correct as of 04/10/2018 when RMS was transferred to BE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0378/001/MR
Name, strength and pharmaceutical form	Kenocidin Chlorhexidine digluconate 5 mg/ml, Teat dip solution for cattle (dairy) (For all CMSs except Spain) Kenocidin 5 mg/g, Teat dip solution for cattle (dairy) Chlorhexidine digluconate (Spain)
Applicant	CID LINES N.V. Waterpoortstraat 2 8900 Ieper Belgium
Active substance(s)	Chlorhexidine digluconate
ATC Vetcode	QD08AC02
Target species	Cattle (dairy)
Indication for use	Teat disinfection as a part of a prevention strategy for mastitis in lactating dairy cows. For the maintenance of good teat skin and teat end condition.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original mutual recognition procedure	24 November 2010
Date product first authorised in the Reference Member State	05 November 2009
Concerned Member States for original procedure	Austria Belgium Bulgaria Cyprus Czech Republic Estonia France Germany Greece Hungary Ireland Italy Latvia Lithuania Luxembourg The Netherlands Poland Portugal Romania Slovakia Slovenia Spain

I. SCIENTIFIC OVERVIEW

Kenocidin Chlorhexidine digluconate 5mg/ml, teat dip solution for cattle (dairy) is authorised for use in cattle (dairy). The product is indicated for teat disinfection as part of a prevention strategy for mastitis in lactating dairy cows. The product is also indicated for the maintenance of good teat skin and teat end condition.

The product contains chlorhexidine digluconate 5.0 mg/ml as an active substance. The product is ready to use as a post-milking teat dip, applied up to two times per day. The product is to be applied topically by dipping each teat to three quarters of its length in a dip cup filled with at least 5 ml of the product.

This application was made in accordance with Article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC (a full application).

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC[1].

II. QUALITY ASPECTS

A. Composition

The product contains the active substance chlorhexidine digluconate and the excipients patent blue V (E131), glycerol, allantoin, isopropyl alcohol, macrogol stearate, guar, mint oil partly dementholised, citric acid monohydrate, sodium hydroxide 30% solution and purified water. The choice of the formulation is justified.

The product is presented in either 1 litre white high-density polyethylene multidose containers (HDPE) with HDPE screw caps and o-ring seals, or 5, 10, 20, 25, 60 or 200 litre blue HDPE multidose containers with HDPE screw-caps and o-ring seals. The overseal on the 200 litres presentation is red. Declarations have been provided indicating that the materials comply with European Pharmacopoeia requirements in respect of suitability for food and pharmaceutical use.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

[1] Summary of Product Characteristics

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance chlorhexidine digluconate solution is an established substance described in the European Pharmacopoeia and a copy of the Certificate of Suitability for this material has been provided. The active substance is manufactured in accordance with the principles of good manufacturing practice. The active substance specifications are considered adequate to control the quality of the material.

All excipients with the exception of patent blue (E131) are described in the European Pharmacopoeia. The applicant has provided detailed in-house specifications for patent blue (E131). A certificate of analysis for all the excipients has been provided.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided.

G. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. The shelf life of the veterinary medicinal product as packaged for sale is 18 months. An in-use shelf life of 6 months is justified.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

A shelf life of 18 months and in-use shelf life of 6 months is justified, subject to the following storage warnings:

- Keep container tightly closed.
- Protect from frost.
- If the veterinary medicinal product has frozen, thaw in a warm place and shake well before use.
- Protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The effects of chlorhexidine salts on the mammalian system have not been discussed by the applicant. The applicant referred to the CVMP[2] summary report for chlorhexidine, which states that chlorhexidine is poorly absorbed after oral or topical application because of its cationic nature. Published information indicates that chlorhexidine is poorly absorbed by the gastrointestinal tract. In humans, a 300 mg dose of chlorhexidine leads to a plasma C_{max} of 0.206 ng/mg at T_{max} 30 minutes after oral administration. Chlorhexidine could not be measured in plasma 12 hours after administration. It is stated that 90% of chlorhexidine is excreted in the faeces and <1% via urine.

Toxicological Studies

3.1 Single Dose Toxicity

A study was carried out on the product according to OECD[3] guideline which indicated a very low toxicity, with an LD_{50} of >2000 mg/kg in rats.

3.2 Repeated Dose Toxicity

The applicant refers to the CVMP summary report, which states that the NOEL[4] for both rats and dogs is 0.5 mg/kg bodyweight.

3.3 Tolerance in the Target Species

The references provided indicate that this product is well-tolerated.

3.4 Reproductive Toxicity (Inc. Teratogenicity)

The applicant refers to the CVMP MRL summary report, which indicates that there is no substance-related effect on mating performance, pregnancy rate or gestation period and that there was no indication of teratogenicity. The NOEL for foetotoxicity was found to be 4.9 mg/kg bodyweight, based on reduced pup weights on day 4 post-partum.

3.5 Mutagenicity

The applicant has provided one reference which states that the active ingredient is non-genotoxic in two mammalian systems, and was equivocal in bacterial systems.

3.6 Carcinogenicity

The applicant refers to the CVMP MRL summary report, which indicates that chlorhexidine is not carcinogenic.

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[2] Committee for Medicinal Products for Veterinary Use
[3] Organisation of Economic Co-operation and Development
[4] No observed effect level

Observations in Humans

The applicant refers to the CVMP summary report which indicates that chlorhexidine has been used in human medicine as an antiseptic and disinfectant for over 40 years. Most preparations are intended for topical use and contain up to 4% chlorhexidine gluconate. The incidence of adverse reactions is low and involves mostly irritation of the skin, eye and mucosa and hypersensitivity reactions. No adverse effects were observed following the oral administration of 2g/day chlorhexidine hydrochloride to human volunteers for 7 consecutive days.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline addressing the potential exposure routes to the operator. The following warnings and precautions as listed on the SPC and product literature are adequate to ensure safety to users of the product:

- Avoid contact with eyes. If splashed in the eye, rinse with clean running water and seek medical advice.
- In case of ingestion, drink large quantities of water and seek medical attention immediately.
- Keep away from food and animal feed.
- Wash hands after use.
- People with known hypersensitivity to chlorhexidine should avoid contact with the veterinary medicinal product.
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Ecotoxicity

The applicant has provided a Phase I environmental risk assessment in compliance with the relevant guidelines. Kenocidin is indicated for use twice daily in milking cows. It is applied topically to each teat by dipping. Absorption of the active substance will be negligible, and chlorhexidine will reach the environment by dripping from teats shortly after treatment and possibly by mechanical transfer onto bedding and/or pasture.

The PEC_{soil}[5] calculations provided indicate that exposure will not be extensive. There is no requirement for further assessment in Phase II. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[5] Figure provided after calculation of the predicted concentration of active substance in the upper 5 cm of soil.

III.B Residues documentation

The applicant has not provided any residue depletion studies in support of this application
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The CVMP summary report indicates that levels up to 78 µg/L had been found in milk after treatment with a similar product after each milking for 20 weeks. Taking into account the European food basket approach, 1.5 L milk could be consumed by a person in a day, 78 x 1.5 = 117 µg, much less than the ADI[6]. The final conclusions of the EMEA CVMP summary report for chlorhexidine states that the chlorhexidine is poorly absorbed after oral and topical administration, it is of low toxicity, and residues in milk from its use as a teat dip or spray have been demonstrated to be low.

Withdrawal Periods

The following withdrawal periods are listed on the SPC and product literature:
Meat and Offal: Zero days.
Milk: Zero hours

[6] Acceptable Daily Intake

IV CLINICAL ASSESSMENT (EFFICACY)

Pharmacology

The applicant has provided a number of bibliographic references to support the pharmacodynamics of chlorhexidine. Its use is well-established as an antiseptic since 1969. It is widely used in antiseptic products, hand washes and oral products, and as a disinfectant and preservative.

Chlorhexidine is a biguanide antiseptic which targets the cytoplasmic membrane of non-sporulating bacteria and yeast causing generalised membrane damage involving the phospholipid bilayers. Low concentrations affect plasma membrane integrity causing cytoplasmic leaking, but are insufficient to induce lysis or death. High concentrations cause congealing of cytoplasm (precipitation of proteins and nucleic acids) with less leakage, but a quicker rate of germicidal activity is noted. The agent crosses the cell wall or outer membrane probably by passive diffusion.

Chlorhexidine is a bactericidal agent with a broad spectrum of activity. Bacteria and yeasts rapidly take up the chlorhexidine and the maximum effect can be seen within 20 seconds. Chlorhexidine is not sporicidal, but it prevents the development of bacterial spores. It inhibits spore outgrowth but not germination. It is reported to be mycobacteriostatic for some species with inhibitory effects probably not dissimilar to those on susceptible bacteria, but generally mycobacteria are highly resistant to chlorhexidine. The latter is possibly due to the waxy cell wall which prevents adequate biocide entry.

A test was conducted according to validated standard EN1040 to determine the basic of bactericidal activity. Solutions containing 80%, 40% and 20% of the final formulation were tested for 5 minutes against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. From the test report it was concluded that kenocidin was bactericidal even at 20 % of its normal strength at 36^0C. Another test was conducted for 5 minutes and 30 minutes at 37^0C using reconstituted milk against *Pseudomonas aeruginosa*, *S. aureus*, *Proteus vulgaris* and *Enterococcus hirae* according to the validated standard EN1656. The test report concluded that kenocidin was bactericidal at 20% of its normal strength in 30 minutes and 5 minutes. A test was also conducted according to the validated standard EN1656 for 5 min at 37^0C with 10g/l skimmed milk solution against *Citrobacter freundii*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Streptococcus bovis*, *Corynebacterium bovis*, *Escherichia coli*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* and *Streptococcus uberis*. The study concluded that kenocidin was bactericidal at 40% of its normal strength at 30^0C with 5 minutes contact time with skimmed milk.

Pharmacokinetics

The applicant submitted literature references which demonstrate that chlorhexidine is not significantly absorbed through the skin after topical application and therefore no systemic pharmacokinetic activity is indicated.

Tolerance in the Target Species of Animals

Local tolerance has been demonstrated sufficiently in the field study. At one site, the majority teat skin and end scores were between 1 and 2, which indicates that the worst affected teats were showing some evidence of scaling but no chapping or cracking. The teat ends had a raised ring, but were not red or cracked, which demonstrated that the teats were being maintained in good condition. At another site the teat and hyperkeratosis scores were comparable between the final formulation and the positive control, which has established local tolerance. Again, teat skin score was maintained between an acceptable 1 and 2. This trial took place from the end of winter to the beginning of summer, therefore local tolerance is considered acceptable in all seasons.

Resistance

The data submitted by the applicant demonstrate that chlorhexidine is a bisbiguanide antiseptic**.** Chlorhexidine has a broad-spectrum efficacy. It is capable of rapidly and completely killing on contact the majority of all vegetative bacteria, and there is no known mechanism of resistance to chlorhexidine as a topical antiseptic.

IV.B Clinical Studies

The applicant has provided literature evidence of the effectiveness of chlorhexidine teat dips to control numbers of new intramammary infections and to keep teats in good condition, and has provided a multicentric field efficacy trial using the final formulation. The applicant has justified their inclusion of 0.5 % chlorhexidine and the emollient combination (5.3%), via bibliographic evidence which shows chlorhexidine is included in teat dips at 0.4 % to 2 % throughout the EU, and that emollients are included without adverse effects on efficacy at 4 % to 6 %. The applicant has submitted several references which demonstrate the efficacy and local tolerance of 0.5 % w/w chlorhexidine teat dips, some of which contained similar levels of emollient. One field study comparing the final formulation to two positive controls has shown that kenocidin was as efficacious as authorised products and supports maintenance of good teat condition.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)