ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Kenostart 3 mg/g Teat dip Solution for Cattle (dairy)

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/0229/001/MR
Name, strength and pharmaceutical form	Kenostart 3 mg/g Teat dip Solution for Cattle (dairy)
Applicant	CID Lines NV Waterpoortstraat, 2 8900 IEPER Belgium
Active substance	Iodine
ATC Vetcode	QD08AG03
Target species	Cattle
Indication for use	Teat disinfection as part of a prevention strategy for mastitis in cattle

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	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	06th March 2007
Date product first authorised in the Reference Member State (MRP only)	19th January 2006
Concerned Member States for original procedure	Belgium Cyprus Estonia France Germany Greece Ireland Italy The Netherlands Poland Portugal Spain

I. SCIENTIFIC OVERVIEW

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 slight reactions observed are indicated in the SPC.
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.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.
Throughout this assessment report, Kenostart 3 mg/g Teat Dip Solution for Cattle (Dairy), Iodine will be referred to as Kenostart.

II. QUALITY ASPECTS

A. Composition

The active ingredient, iodine, is incorporated into the product in the form of an iodine complex known as an iodophor. In this case, the iodophor consists of sodium bisulphite and sodium iodide, which act as stabilisers, glycerol as an emollient, an alcohol ethoxylate which helps the iodine to dissolve as well as aiding stability of the solution, sodium hydroxide and citric acid to control the pH of the solution, and water as the solvent. The iodophor has been formulated to ensure that the required amount of free iodine will be available throughout the life of the product.

The product also contains xanthan gum to produce a solution of the desired viscosity (thickness), sodium iodate and sodium chloride as stabilisers, citric acid and sodium hydroxide to control the pH, and water as the solvent. Ethoxylated lanolin, glycerol, sorbitol and ethoxylated fatty acid monoethanolamide derived from rapeseed oil are included as emollients.

The container/closure system comprises high density polyethylene (HDPE) drums of various sizes of 1, 5, 10, 20, 25, 60 and 200 litres. Each drum is sealed with an HDPE cap and low-density polyethylene (LDPE) O-ring. The particulars of the containers and controls performed are provided and conform to the European Pharmacopoeia where appropriate, and have been shown to be satisfactory.

The choice of the formulation is justified.

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

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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is iodine, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

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

Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control on intermediate products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Iodine is a simple inorganic substance and is considered inherently stable when stored appropriately and no data have therefore been provided on this aspect. This is considered acceptable.

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 in-use shelf-life of 6 months is supported by the data provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary product as packaged for sale: 16 months
Shelf life after first opening the immediate packaging: 6 months

Storage conditions:

- Store upright in the tightly closed original container
- Protect from frost
- If the 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 basic bactericidal activity of iodine has been demonstrated on numerous occasions and the company submitted an example of the available information on this subject. This document describes the application of two iodophor solutions to infected skin wounds on guinea pigs. The results indicated that these products were effective in dealing with the infection and were non-irritating to the skin.

Iodine has been used in human medicine as part of the treatment for serious burns. In the case described in the company's dossier, it was applied as an ointment. One purpose of the study was to assess how much of the iodine in the ointment was absorbed into the bloodstream in these patients whose skin was severely damaged. Although some iodine was found in the bloodstream in some patients, the amount found did not exceed the amounts normally absorbed from food. It was noted that the product used in this case contained 1% iodine, whereas Kenostart contains only 0.3% iodine. Furthermore, in the case of Kenostart, the product will be applied to a comparatively small area of the body (the teats of cattle) and it would be expected that the skin on these would be in better condition than that of the human burns patients. It can therefore be concluded that absorption of iodine as a result of teat dipping with Kenostart will be negligible.

Toxicological Studies

A study conducted by the company showed that Kenostart is of very low toxicity when administered as a single oral dose to rats.

Published information on the toxicity of iodine when administered to rats in drinking water for 100 days indicates that the main effects were on the thyroid gland and thyroid hormones. This result is expected because iodine is a component of the thyroid hormone, thyroxine. The effects were observed only when the iodine was given in the form of iodide, not when it was given simply as iodine. Another publication indicated that some rats have a genetic predisposition to the development of thyroid disease induced by consuming large quantities of iodine. Studies in young cattle also showed that the main effects of excessive iodine intake were on the thyroid.

The product Kenostart is tolerated well by cattle, as indicated by the studies reported in Section IV of this document.

In published studies, excessive dietary iodine has been shown to have a transient effect on the fertility of rabbits, rats and mink, but not on that of hamsters and pigs. Excessive dietary iodine during pregnancy did not cause malformations in the young, although the thyroid glands and the spleen were larger.

Although iodine has been reported to be capable of causing mutations in bacteria and some other cells in culture, it appears not to cause such mutations in mammals. Because it stimulates the thyroid gland, it is possible that high levels of iodine could be linked to an increased incidence of thyroid tumours. However, there is no good evidence to support this possibility. Indeed, a lack of iodine can have more serious consequences.

The company has conducted a study to investigate if Kenostart is irritant to rabbit skin and another, *in vitro*, study for irritation to eyes. These studies indicated that contact of Kenostart with the eyes might cause irritation.

Iodine has been used extensively in human medicine, both as a disinfectant and to treat thyroid disease, with a low rate of adverse effects.

User Safety

The company gave detailed consideration to the safety of people who might come into contact with Kenostart, mostly farmers, but also possibly vets or children living on the farm. The most likely way in which contact with the product would occur is by splashing or spillage when transferring it from the container to the dip cups and when dipping the teats. It is noted that the product is not attractive to children.

The product is formulated to be gentle and non-corrosive for use on teats that may be sore, and therefore it would not be expected to adversely affect normal human skin. Indeed, studies have shown that it is not irritant to skin although it could be to eyes. It is of low toxicity when administered by mouth and would be less so by skin contact because it is not absorbed into the bloodstream.

As a result of these facts, warnings have been agreed regarding eye contact. Advice has been included regarding accidental ingestion despite the low toxicity, simply because of the general undesirability of consuming such solutions. General warnings to keep the product away from food and animal feed and to wash hands after use have also been agreed. These warnings all appear on the SPC and labelling for the product, and user safety aspects of this product are therefore satisfactory.

The applicant submitted a good user risk assessment and proposed appropriate warnings. The warnings proposed are also in line with other similar products of similar formulation. User safety is therefore considered satisfactory.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

In considering the environmental impact of the use of Kenostart, the company took into account the facts that the product is used routinely in dairy cattle after each milking, it is unlikely to enter the environment directly, it is not absorbed into the animals' bloodstream and is not therefore excreted in urine or faeces, and small quantities of the product may be disposed of by dilution with water.

Data obtained from actual use of the product indicate that around 3 ml of the product is needed to dip all four teats of one animal. Of this, less than 10% dripped off the teats immediately after dipping and just over 11% still remained on the teats by the time of the next milking.

Using this information, predictions have been made of the concentration of iodine that will enter soil (PEC_{soil}) each year, for animals housed indoors, animals on pasture and for waste water containing the product. These concentrations are 21.3, 11.9 and 10.6 micrograms of iodine per kilogram of soil, respectively. The calculations were made in accordance with recognised guidelines.

The company then presented various publications indicating the natural occurrence of iodine in soil. Although this varies considerably, it is usually in excess of 2000 micrograms per kilogram, which is approximately 100 times the PEC values calculated for Kenostart. Thus the contribution of the normal use of Kenostart to total environmental iodine is insignificant and acceptable.

However, iodine is on List II of the Groundwater Regulations 1998, and this means that anyone wishing to dispose to land any unused product containing iodine must have an authorisation to do so. This requirement is reflected in the SPC and labelling of Kenostart.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

Ingredients used in veterinary medicines intended for use in animals which produce food for human consumption must have been assessed by the European Union for the levels which may be permitted in these foodstuffs. As a normal component of the human diet, iodine has been considered from the point of view of whether its use in teat dips increases the amount of consumed iodine to unacceptable levels. The result of this consideration was that it does not, and it has therefore not been necessary to establish maximum residue limits (MRLs) for this ingredient. In addition, it has not been considered necessary to establish MRLs for any of the other ingredients of Kenostart.

The company submitted some published data which supports the conclusion that residues of iodine in meat or milk from treated cows do not present a risk for consumers and that no withdrawal period is necessary. This means that it is safe to eat meat from animals slaughtered immediately after teat dipping (although this is unlikely to happen in practice) and to drink milk collected from animals at the next milking after teat dipping.

MRLs

Iodine is listed in Annex II of Council Regulation 2377/90 and is being used in accordance with the provisions of its Annex entry

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat, offal and milk in cattle is justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The company provided a collection of published scientific papers on the use of iodine as a disinfectant teat dip. These papers provide the background to the rationale behind the formulation of Kenostart by demonstrating the effectiveness of iodine and the importance of constant levels of free iodine. The mode of action of iodine is thought to be by oxidation of bacterial components. The papers also point to factors which may affect the efficacy of iodine when used in teat dips, e.g. temperature changes, pH of solution, the presence of milk, dirt, straw, etc.

The company supplemented this information with a series of studies conducted by themselves, in accordance with European guidelines, to demonstrate the basic bactericidal activity of Kenostart. In these studies, cultures of various bacteria which may cause mastitis were exposed to Kenostart for five minutes, and the degree of bacterial killing was noted. These studies showed that all the bacteria were effectively killed, even when the product was used at only 40% concentration, and in the presence of milk.

Pharmacokinetics

The company provided published literature which showed that iodine coated onto the skin rapidly interacts with any organic material present leaving very little free iodine for absorption through the skin. Therefore, no further information on the amount of iodine entering the bloodstream is required.

Tolerance in the Target Species of Animals

The company submitted the results of two field trials in which Kenostart was used as a post-milking teat dip. In the first of these studies, which took place in spring/early summer, a group of Jersey cows with no evidence of mastitis were treated with Kenostart for ten weeks, and a further group of similar cows were treated with an established product. The teats of each cow were examined immediately after milking and somatic cell counts (which can be linked with mastitis) were monitored on a monthly basis. There was no significant difference in teat condition, somatic cell count or incidence of mastitis between the two groups of animals.

The second study took place in winter, when temperatures were much lower, and involved the treatment of a number of Holstein cows with Kenostart. Teat condition improved over the course of the trial. These two studies support the published literature which indicate that iodine teat dips formulated in a similar way to Kenostart are well-tolerated by lactating cows and indeed improve teat condition.

Resistance

The information provided suggests that all types of bacteria appear to be currently sensitive to the oxidative action of iodine. There is no known resistance mechanism to this oxidative action.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Field Trials

In addition to published information on iodine teat dips, and the two studies described in the preceding section, the company submitted the results of two field trials in which Kenostart was used as a post-milking teat dip for Holstein cows. Both these studies were conducted in winter when the weather was cold and wet. Teats were examined at regular intervals (2 weeks in one study and 4 weeks in the other) and somatic cell counts were also monitored. There was no significant difference in the teat condition at the end of either study. In the first study, somatic cell counts were similar during the period of the study to what they had been during the same period in the previous year. In the second study, somatic cells were considerably lower than they had been during the same period in the previous year and also lower than they had been during the three months prior to the start of the trial.

These two studies demonstrated that the product was well tolerated, maintaining teat condition during the trial periods and either reducing or not adversely affecting somatic cell counts. There was a low incidence of mastitis in both cases.

Because the published literature shows that the effectiveness of iodine may be affected by temperature, the study conducted during spring/early summer (described in the section on tolerance) and some additional published literature were also taken into consideration in the overall assessment of efficacy. This information showed that the product was efficacious at the warmer temperatures of spring and early summer as well as in winter.

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 risk benefit 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.

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