ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Kenostart Spray and Dip 3 mg/g Teat Dip or Spray Solution for Cattle (dairy)
(For all CMS except France and Sweden)

Kenospray 3000, 3 mg/g Teat Dip or Spray Solution for cattle (dairy)
(France)

Kenospray vet., 3 mg/g Teat Dip or Spray Solution for cattle (dairy)
(Sweden)

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/0244/001/MR
Name, strength and pharmaceutical form	Kenostart Spray and Dip 3 mg/g Teat Dip or Spray Solution for Cattle (diary)
Applicant	CID Lines NV
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 32(2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	04 January 2008
Date product first authorised in the Reference Member State (MRP only)	6 September 2007
Concerned Member States for original procedure	Austria Belgium Cyprus Estonia France Germany Greece Ireland Italy Netherlands Poland Portugal Spain Sweden

I. SCIENTIFIC OVERVIEW

Kenostart Spray and Dip 3 mg/g Teat Dip or Spray Solution for Cattle (dairy) is a teat dip solution containing iodine for disinfecting the teats of cattle after milking, as an aid in the prevention and control of mastitis. Mastitis is a common disease in which the udder is inflamed and it can cause considerable pain. Even if there are no obvious signs of disease, mastitis can reduce milk yields by around 10% and it is therefore of economic, as well as animal welfare, importance.

The disease may be caused by a number of different micro-organisms and is therefore treatable with antibiotics. However, prevention is preferable, and may be achieved by practising good teat hygiene. Iodine has long been known as an antiseptic, and regular cleaning of the teats with this substance can help to ensure that harmful organisms do not enter the teat canal.

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[1]. 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.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance iodine and excipients glycerol, sorbitol 70%, sodium hydrogen sulphite 40%, ethoxylated lanolin 50%, sodium iodate, sodium chloride, sodium hydroxide 30%, sodium iodide, xanthan gum, alcohol (C12-C15) 11 mole ethoxylate, citric acid and water purified.

The product is supplied in high-density polyethylene (HDPE) drums of various sizes, ranging from 1 to 200 litres. Each drum is sealed with an HDPE cap and low-density polyethylene (LDPE) O-ring, and the solution is ready to use without dilution. It is intended to be used immediately after milking by either dipping each teat into a teat cup containing at least 5 ml of the product, or by spraying each teat and replenishing the sprayer as necessary.

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.

[1] Summary of Product Characteristic

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 iodine an established substance described in the European Pharmacopoeia. The iodine is obtained by the company for manufacture of the product, and the company carries out an identity test on receipt of this simple inorganic molecule. The active substance specification is considered adequate to control the quality of the material.

All other substances also comply with European Pharmacopoeial monographs where these exist. In other cases, the company has created its own specifications and these, and the analytical methods used to check that they are being met, are appropriate for this product. In particular, the ethoxylated lanolin and alcohol (C12-C15) 11 mole ethoxylate comply with EU guidance on the use of ethylene oxide in the manufacture of medicines.

The company's specifications for the HDPE containers and caps and the LDPE O-rings include reference to the European Pharmacopoeia where appropriate, and have been shown to be satisfactory.

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 three 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

Active substance

As iodine is a simple inorganic substance, it is considered inherently stable when stored appropriately, and no data have therefore been provided on this aspect.

Intermediate Product

The company provided data on three batches of the iodophor, stored for eight weeks under different conditions of temperature and humidity. These demonstrated that this intermediate product may be stored for eight weeks.

Finished Product

Stability studies have been undertaken on three batches of the product stored in several different sizes of container, at temperatures ranging from below freezing to 40°C and at two different humidity levels. On the basis of the results of these studies, a shelf-life of 2 years was approved for the product. Because the study on freezing and thawing was limited to 3 days, a warning to protect from frost was considered appropriate. The study also showed the importance of thawing frozen product thoroughly and shaking well before use to ensure that it is homogeneous. None of the studies investigated the effect of light on the product and, although the containers are opaque HDPE, a warning to protect from light has also been approved.

In-Use

Similar studies using three batches of product stored in opened containers demonstrated that the product is stable for 6 months under these conditions.

The supporting data demonstrate that the teat dip is suitably formulated and quality-controlled. A shelf-life of two years is justified, as is an in-use shelf-life of 6 months, subject to the following warnings:

- Store in the original container
- Keep the 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 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 the proposed product 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 the product will be negligible.

Toxicological Studies

A study conducted by the company showed that the product 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 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 the product is an irritant to rabbit skin and another, *in vitro*, study for irritation to eyes. These studies indicated that contact of the product 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 the product, 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 or sprayer, 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 an 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.

Ecotoxicity

In considering the environmental impact of the use of the product, 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 the product. Thus the contribution of the normal use of the product 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 the product.

III.B Residues documentation

Substances 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 substance. In addition, it has not been considered necessary to establish MRLs for any of the other substances contained in the product.

The company submitted some published data which support 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.

Withdrawal Periods

A withdrawal period of zero days for meat and offal and zero days for milk are 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 the product 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 the solution and 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 the product. In these studies, cultures of various bacteria which may cause mastitis were exposed to the product 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 20% 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 three field trials in which the product was used as a post-milking teat dip and spray, one in the UK and two in Belgium. In the first of these studies, which took place in spring/early summer, 15 Jersey cows with no evidence of mastitis were treated with the product for ten weeks, and a further 15 similar cows were treated with an established product.

The first Belgian study took place in winter, when temperatures were much lower, and involved the treatment of 30 Holstein cows with the product. Teat condition improved over the course of the trial. The second trial took place late winter/ early spring when the temperatures were more average, and involved the treatment of 34 lactating Holstein dairy cows. Teat condition improved over the course of the trial. These three studies support the published literature which indicate that iodine teat dips formulated in a similar way to the product are well-tolerated by lactating cows and indeed improve teat condition. 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.

Resistance

All types of bacteria currently appear to be sensitive to the oxidative action of iodine. There is no known resistance mechanism to this oxidative action.

IV.B Clinical Studies

In addition to published information on iodine teat dips and sprays, and the three studies described in the preceding section, the company submitted the results of three Belgian field trials in which the product was used as a post-milking teat dip for Holstein cows. The first two studies were conducted in winter when the weather was cold and wet, however the final study was conducted over a six month period and incorporated winter, spring and summer weather. Teats were examined at regular intervals (2 weeks in one study and 4 weeks in the other two) and somatic cell counts were also monitored. There was no significant difference in the teat condition at the end of the studies. 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. In the third study the somatic cell counts fluctuated between periods of the trial, but overall there was no significant difference between the somatic cell counts of each year.

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

Because the published literature shows that the effectiveness of iodine may be affected by temperature, the study conducted in the UK (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 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)