ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bovidip 2% w/v Concentrate for Teat Dip or Spray Solution

PuAR correct as of 22/06/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0331/001/MR
Name, strength and pharmaceutical form	Bovidip 2% w/v Concentrate for Teat Dip or Spray Solution
Applicant	DeLaval NV Industriepark-Drongen 10 9031 Gent B-9031 Belgium
Active substance(s)	Iodine 2 % w/v
ATC Vetcode	QG52A
Target species	Cattle
Indication for use	Teat disinfection as an aid in the prevention of mastitis in lactating dairy cows.

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 13a of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	29 October 2008
Date product first authorised in the Reference Member State (MRP only)	9 July 2007
Concerned Member States for original procedure	Belgium Ireland Netherlands

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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, 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 include purified water, glycerol, macrogol lauryl ether, poloxamer 335, sodium iodide, citric acid monohydrate and sodium hydroxide. The applicant has included literature

references to show that iodine is an effective, extensively studied disinfectant. There are many similar products available.

The product is presented in grey high-density polyethylene (HDPE) bottles containing 5, 10, 20, 60 and 200 litres of the dip. The closures are formed from HDPE and comprise screw-fit caps with o-ring seals. The caps and o-rings are black for the 5, 10, 20 and 60 litre pack sizes but for the 200 litre pack size the cap is white and the o-ring is red. 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.

The particulars of the containers and controls performed are provided and conform to the regulation.

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.

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

C. Control of Starting Materials

The active substance, iodine, is an inorganic molecule manufactured by a simple extraction process. The active substance and all the excipients are all well characterised and all comply with the appropriate European Pharmacopoeial monographs. 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

A TSE declaration and accompanying format 3 tables were provided.

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. Due to the strong antibacterial properties of the product, microbiological quality testing on the final product is not required. Data have also been provided to show that viscosity is not a critical parameter for use of the product, hence viscosity testing has also been omitted. The tests include appearance, identification of iodine, assay of iodine, pH and density. 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

No stability data have been provided for iodine but due to the inorganic nature of the material, as long as it is properly stored once manufactured, its composition should not change. The omission of stability data for the active substance is considered acceptable in this case.

The proposed stability specification for the iodine complex is the same as that for its manufacture. Studies have been undertaken on three full scale 500 kg batches of the iodine complex and the duration of the studies was two months with results produced at the initial, month one and month two time points. The storage conditions were 25°C/60% RH and ten litre samples were stored in the containers of the same construction as the intermediate bulk containers i.e. HDPE. The stability data support the proposed 2 month shelf life.

Stability data have been generated on three batches of the finished product. The applicant has stated that the containers used are of the same specification as the commercial containers. It is proposed that these batches will be stored for up to 24 months at 25°C/60% RH and six months at 40°C/75% RH. At this stage, data have been generated for up to 24 months for the laboratory batch and 24 months and 18 months for two pilot batches.

The stability data at 25°C/60% RH and 40°C/60% RH show that the lower shelf life assay limit for available iodine is justified. These data indicate that the product should not be stored at more than 25°C. Based on the data available, currently a 24 month shelf life when stored below 25°C is justified.

No photostability studies have been undertaken but this is justified as iodine is well known to be sensitive to UV light and hence the product is presented in opaque HDPE containers. The SPC includes the warnings “Protect from light” and “Store upright in the tightly closed original container” and this is considered satisfactory.

The applicant has proposed a warning for the SPC stating, “If the product has frozen, thaw in a warm place and shake well before use.” Data have been

provided for two batches of the product that has undergone three freeze/thaw cycles (-12°C for 16 hr, thaw for 8 hr) and the comparison between initial and final results show that the product may be frozen and thawed without any adverse effect on product quality.

The stability data at 25°C/60% RH show an in use shelf life of six months is justified when stored below 25°C.

No data have been provided on diluted product stability and section 4.9 of the SPC recommends that fresh solution be made up daily. Stability data are only required if it is proposed that the diluted product may be stored for any longer than the day it was produced.

H. Genetically Modified Organisms

None

J. Other Information

Shelf life: 24 months
In use shelf life 6 months

Storage conditions:

Do not store above 25°C.
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. For the larger pack sizes, the product should be rolled sufficiently to mix the solution. Under no circumstances should an attempt be made to shake the 60 or 200 litre packs.
Protect from light.
Diluted product should not be stored in plastic containers.
Prepare fresh solution daily. Discard any remaining solution at the end of the day.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

The applicant has provided various studies, covering all the sections required for Part III. There are already many 0.5% iodine teat dips available and there is reference made to the studies submitted for other authorised iodine teat dips.

III.A Safety Testing

Pharmacological Studies

Iodine is an essential trace element in human nutrition, necessary for the formation of thyroid hormones, and consequently it is used in iodine deficiency

and thyroid disorders. Iodine has bactericidal activity and is used widely as an antiseptic and disinfectant. It works by binding indiscriminately to bacterial membranes, and also inhibits enzymes.

The applicant has presented studies showing how iodine is absorbed and distributed via different routes of exposure (oral, inhalation, topical, eyes). Elimination (when not taken up by the thyroid) is mainly via urine, with small amounts appearing in faeces, saliva and sweat. Iodides can also cross the placenta and are excreted in breast milk.

Some of the references submitted show that absorption of iodine into the skin from the teat surface of milking cows is low. It is concluded that a topically applied iodine-containing product such as this will not be absorbed systemically to any great degree, but that it is possible that small amounts of iodine could get into the milk via one or two routes.

The applicant has provided bibliographical data findings, these are reflected in the SPC.

Iodine solutions react with the organic matter of bacteria and viruses to render them harmless. The mechanism of kill appears to be due to an oxidative-reductive reaction, involving various cell wall constituents, which are irreversibly transformed. The sulphydryl linkages, in bacterial cell wall components, are specifically targeted by iodine.

Literature suggests that absorption of iodine through the skin is well below levels which would lead to pharmacokinetic activity in the body.

Toxicological Studies

Studies have been presented demonstrating the safety of the administration of one dose in rats, and the repeated administration of one dose in rats and in the target animal. Results indicated that iodine has been shown to be toxic at very large doses, however these levels would never be reached with this product. As the iodine will not be absorbed systemically it will not accumulate in the animals.

As far as tolerance in the target species, the product appears to be well tolerated by cattle. Details of the tolerance study can be located in part IV of this report.

The applicant has also provided satisfactory references to studies relating to reproductive toxicity, embryotxicity/foetotoxicity mutagenicity and carcinogenicity.

Other Studies

The applicant has submitted results of an *in vitro* acute ocular irritation test which indicate that the test substance could be an irritant to the eyes. Appropriate warnings are included on the SPC. Results of an *in vitro* acute dermal irritation test are also included. The results indicate that the test substance is not classified as a skin irritant.

Observations in Humans

Varying concentrations of iodine solutions have been used as antiseptics in human medicine and iodine is also an important micronutrient for both humans and animals.

Microbiological Studies

Although no specific studies on human gut flora and organisms used in food processing are reported, both the residue studies and the well-established use of such iodine teat-dips suggest that there is no concern over the effects of the use of this product on these matrices.

Studies on metabolites, impurities, other substances and formulation

Iodine is not metabolised in the body – it is concentrated in the thyroid and incorporated into thyroid hormones. Excess iodine is excreted via the urine. The purity grade of the iodine used in this product is 99.5 % - 100.5 %, so there are no concerns over impurities.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. The user risk assessment covers all possible scenarios
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Care should be taken to avoid eye contact. In case of eye contact, flush the eyes with copious amounts of water and seek medical advice. In case of ingestion, drink large quantities of water and obtain medical attention as soon as possible. When used as spray, avoid working in spray mist. Wash hands after use. Persons with iodine allergy should wear gloves and mask.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Iodine could potentially reach the environment by dripping from teats shortly after treatment and possibly by mechanical transfer onto bedding and/or pasture.

The natural soil content of iodine ranges widely, but is usually in excess of 2000 μg/kg.

The applicant has provided an acceptable estimate of the predicted environmental concentration in the soil (PEC_{soil}) of iodine which indicates that

exposure of the environment will not be extensive. The annual PEC_{soil} value of 67μg/kg is two orders of magnitude lower than natural levels of iodine in soil. Even if all the iodine on the teats was lost to the soil the resulting PEC_{soil} would be significantly lower than the natural soil content.

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

When topically applied onto the teats of cows, iodine may be absorbed through the skin and result in potential residues in the milk. Provided that the product is used within the proposed recommendations there is little risk of significant contamination of milk with iodine residues.

MRLs

Iodine is listed in Annex II of Council Regulation 2377/90. All of the ingredients other than the excipient magrocol lauryl ether contained in this product have an Annex II entry in Regulation 2377/90, and are used in accordance with the provisions of the Regulation. The applicant has provided a study to justify the use of magrocol lauryl ether. The report concluded that there were no effects at any dose level, therefore the use of this excipient at the level found in this product has been justified. As a result, no residue depletion study is submitted.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for both meat and for milk are justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has supported the clinical efficacy of Bovidip 2% Concentrate for Teat Dip and Spray Solution, by providing 4 different types of evidence:

- The *in vitro* germicidal efficacy is shown using the actual formulation that is to be marketed.
- An in-house clinical trial conducted using reference products is submitted. The applicant justifies that this study is relevant to Bovidip 2% w/v Concentrate for Dip or Spray Solution because the ready-to-use solution of their product has the same concentration of active ingredient present as the well-established use reference product

- Many published clinical trials using 0.5% iodine containing teat dip/spray formulations are presented.
- 2% iodine containing teat dip/spray formulations with ready-to-use solutions of 0.5 % have a well-established use in the European Community. The applicant indicates that their product is efficacious based on these similar well-established use products which have been successfully marketed.

The pharmacodynamics and mode of action of iodine and iodophors have been demonstrated adequately. As this is a topical preparation with minimal absorption, pharmacokinetics has not been demonstrated; this is appropriate. The applicant has presented literature to support *in vitro* and *in vivo* antibacterial activity. The bacteriocidal action of this product has much faster kinetics than in the presented literature.

Tolerance in the Target Species of Animals

The applicant has supported target species tolerance of iodine containing teat dips/sprays in three different ways. Firstly, there are several teat dips containing the same ingredients in the same concentrations as the Bovidip 0.5% w/w Teat Dip or Spray Solution formula and these have well-established use within the EU. Secondly, specific trials have been conducted to evaluate these well-established products, specifically for daily use and for effect on teat skin. Lastly, teat dip efficacy studies have been conducted and the effect of the teat dip on teat skin was monitored.

Supportive evidence of the efficacy of the 0.5% iodine in teat dips/sprays was provided. This evidence is considered adequate to demonstrate the efficacy and target species safety of the active substance and Bovidip 2.0 % formulation.

Resistance

The applicant states that all types of bacteria are susceptible to the oxidative action of iodine and that there is no known resistance mechanism. References have been presented to support lack of resistance against iodine. An expert confirms that the mode of action of iodine is targeted at proteins and the respiratory chain of microorganisms. This is a chemical, not biological, rapid killing. It does not involve specific developmental or reproductive mechanisms in one or other types of microorganisms and therefore resistance against iodine does not occur.

IV.B Clinical Studies

The applicant justifies that *in vitro* testing, field trials, scientific literature and the well established use in the EU support the efficacy of this product.

The applicant produced documentation from several field trials, which they justify cover a range of housing, management, environmental and climatic conditions.

The efficacy for Bovidip 2% w/v Concentrate for Teat Dip or Spray Solution is supported. The applicant has presented literature to support *in vitro* and *in vivo* antibacterial activity. Another trial supports efficacy for a well-established product containing 0.5 % iodine. This is the same active substance concentration as in Bovidip 2% w/v Concentrate. Dose determination for the active ingredient, 0.5 % iodine, is supported by a number of trials and justified by the applicant. Dose confirmation of the active ingredient, 0.5 % iodine, under natural conditions is also supported. The applicant and the expert have highlighted the fact that there are many 0.5 % iodine teat dip concentrates which are diluted for use at 0.5 % iodine solutions and therefore support efficacy and local tolerance through well-established use and in all seasons. This is in accordance with the Notice to Applicants Volume 6A. The data presented show that many different formulations of iodine and glycerol have shown efficacy and safety, therefore it is likely that this product will be efficacious and safe.

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.

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