College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Intra Hoof-Fit Gel 40 mg/g + 40 mg/g gel for dairy cattle

NL/V/0173/001

April 2014

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0173/001/MR
Name, strength and pharmaceutical form	Intra Hoof-Fit Gel 40 mg/g + 40 mg/g gel for dairy cattle
Applicant	Intracare BV Voltaweg 4, 5466 AZ, Veghel The Netherlands
Active substance(s)	Copper (as copper diammonium EDTA) Zinc (as zinc diammonium EDTA)
ATC Vetcode	QD03
Target species	Dairy cattle
Indication for use	For use as part of a treatment programme of digital dermatitis.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	A mutual recognition application in accordance with Article 13b of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	20 February 2013
Date product first authorised in the Reference Member State (MRP only)	23 February 2012
Concerned Member States for original procedure	DK, EE, FR, LT, LU, LV, SE, UK

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 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 40.0 mg/g copper (as diammonium EDTA) and 40.0 mg/g zinc (as diammonium EDTA) and the following excipients: tartrazine E102,

carmellose sodium, glycerol, sodium starch glycolate (type C), purified water and isopropyl alcohol.

The container/closure system consists of a 350 ml PP jar with a HDPE screwlock cap. The target fill-weight is 430 g. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

C. Control of Starting Materials

The active substances are copper diammonium EDTA and zinc diammonium EDTA, both are novel active substances that are not described in the European/British Veterinary Pharmacopoeia. The active substances are 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 on three batches per drug substance.

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

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

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

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 claim of 1 month stability after broaching is based on the demonstration of stability for a batch broached and stored for 30 days at ambient temperature.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that Copper has antimicrobial properties and a positive effect on wound healing while Zinc stimulates wound healing and has a mild antimicrobial effect against gram positive bacteria.

The applicant has also provided bibliographical data which show that possible absorbed amounts of copper are bound by weak bonds to albumin in blood plasma and stored in the liver. Excess of copper is excreted via bile, a small percentage via urine and partly via milk. Possible absorbed amounts of zinc are mainly excreted via bile (80%), partly via urine and partly via milk.

Toxicological Studies

The applicant has provided bibliographical data which show that copper and zinc are normal constituents of the diet and as such relatively safe. Concentrations of copper and zinc that would cause chronic poisoning are not reached during treatment with the product. EDTA salts are poorly absorbed from the gastrointestinal tract while they are rapidly and completely eliminated into the urine after parenteral injection. It is concluded that the percutaneous absorption of copper, zinc and EDTA will be very low, and most probably negligible. If absorbed it will be excreted rapidly and completely.

Observations in Humans

The applicant has provided bibliographical data which show that copper intoxication results in gastrointestinal disturbances and eventually liver and kidney damage. Copper is not classified as a human carcinogen by EPA as there are no adequate studies available. The applicant has provided bibliographical data which show that Zinc has low acute toxicity after oral and inhalation exposure.

Microbiological Studies

The applicant has provided information which shows that copper exerts its bactericidal or bacteriostatic effects through different mechanisms including substitution of essential ions and blocking of functional groups of proteins, inactivation of enzymes, production of hydroperoxide free radicals and alterations of membrane integrity. The applicant has provided information which shows that Zinc exerts a mild antimicrobial effect, mainly on gram positive bacteria. Treponema, the bacterial species associated with Digital Dermatitis is gram negative, therefore the antimicrobial effect of the product is mainly caused by the Copper content.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that absorption of active ingredients after dermal contact with the product is none and no dermal irritations are expected. The product may cause eye irritation. The risk of exposure is however small, the product has a high viscosity which reduces the risk of ocular exposure, while the risk of dermal exposure is small as the product is applied with a brush and is only used by professionals.

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

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the amounts of copper, zinc and EDTA entering the environment will not be harmful.

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

No residue depletion studies were conducted because Copper salts, Zinc salts and EDTA salts as well as the excipients isopropyl alcohol, glycerol and carboxymethyl cellulose are included in Annex II of the Council regulation No 2377/90 (no MRL required). The excipient Sodium Starch Glycolate is included in the 'out of scope list' with the remark 'for cutaneous use only' this complies with the use of the product.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat in cattle and 0 hours for milk are justified.

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

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

Bibliographical data have been provided which show that the product contains no harmful substances and the actives are not absorbed through the skin. As it is plausible that the product is not harmful to cattle when used as intended, it was concluded that no target species tolerance study was necessary.

Resistance

The information provided suggests that copper and zinc resistance has not been reported despite extensive use in farming industry and is therefore unlikely to occur. The product is unlikely to contribute to development of resistance as the

concentration of copper is significantly higher then the Minimum Inhibitory Concentration.

IV.B Clinical Studies

Laboratory Trials

The applicant has provided information which shows that the concentration of Copper and Zinc is limited by the chemical process. The product contains maximum amounts of copper and zinc. As a maximum concentration of the actives will lead to maximum clinical effects, dose determination studies were not performed.

Field Trials

The applicant has conducted field studies which show that the product is efficacious and safe.

A controlled multicentre field study was performed in 2009-2010 in the Netherlands. The experimental unit was a hind leg with a Digital Dermatitis M2 lesion; 102 hoofs were treated with the positive control product (Chlortetracyclinehydrochloride spray), 103 hoof were treated with the product and bandaged. Transition of an M2 lesion to a M0, M1, M3 or M4 lesion at Day 28 was considered a cure. At day 28, 58% of the control-treated legs were cured whereas 92% of legs treated with the product were cured showing significantly better cure rate after treatment with the product compared to the positive control. One adverse event (swelling) after treatment with the product was reported at day 1, which had disappeared at day 3. No further adverse events were reported therefore it can be concluded that the product is safe.

Two non-controlled clinicals trial were performed on dairy farms in the Netherlands and in Iran. Different treatment schedules were used and as these were non-controlled studies, no conclusions can be drawn from the results.

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 Heads of Vetrinary Medicines Agencies website (www.HMA.eu).

This section 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.

March 2017	Renewal procedure – End of Procedure 23 February 2019
November 2017	Change in manufacturer and API specs. Type II: B.I.a.1.g; Type II: B.I.b.1.f; Type IAin: B.II.b.1.a; Type IAin: B.II.b.1.b; Type IB: B.II.b.1.e: Type IAin: B.II.b.2.c.2