Veterinary Medicines Directorate

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Topimec Plus 10/100 mg/ml Solution for Injection for Cattle (UK, PT)
Levatum Super 10/100 mg/ml Solution for Injection for Cattle (BE)
KARIMECTIN PLUS 10/100 mg/ml Solution for Injection for Cattle (ES)
Levatum Plus 10/100 mg Solution for Injection for Cattle (IT)
Levatum Fluke 10/100 mg/ml Solution for Injection for Cattle (DE)
Animec D 10/100 mg/ml Solution for Injection for Cattle (FR)

PuAR correct as of 14/03/2019 when RMS was transferred to PT. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0399/001/MR
Name, strength and pharmaceutical form	Topimec Plus 10/100 mg/ml Solution for Injection for Cattle
Applicant	Chanelle Animal Health Ltd
Active substance(s)	Clorsulon, Ivermectin
ATC Vetcode	QP54AA51
Target species	Cattle
Indication for use	The product is indicated for the treatment of mixed infestation of adult liver fluke and gastro-intestinal roundworms, lungworms, eye worms, and/or mites and lice of beef and non-lactating dairy cattle. **Gastrointestinal roundworms** (adult and fourth-stage larvae): *Ostertagia ostertagi* (including inhibited larval stages) *O. lyrata* *Haemonchus placei* *Trichostrongylus axei* *T. colubriformis* *Cooperia oncophora* *C. punctata* *C. pectinata* *Bunostomum phlebotomum* *Oesophagostamum radiatum* *Strongyloides papillosus* (adult) *Nematodirus spathiger* (adult) *Nematodirus helvetianus* (adult) *Trichuris spp* (adult) **Lungworms** (adult and fourth-stage larvae) *Dictyocaulus viviparus* **Liver fluke** (adult): *Fasciola hepatica*

	Eye worms (adult): *Thelazia spp* **Warbles** (parasitic stages): *Hypoderma bovis* *H. lineatum* **Mange mites:** *Psoroptes bovis* *Sarcoptes scabiei* var. *bovis* **Sucking lice:** *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus.* The product may also be used as an aid in the treatment of biting lice (*Damalinia bovis)* and the mange mite *Chorioptes bovis*, but complete elimination may not occur. **Persistent activity** The product given at the recommended dosage of 1ml/50kg bodyweight controls re-infection with *Haemonchus placei, Cooperia* spp. and *Trichostrongylus axei* acquired up to 14 days after treatment, *Ostertagia ostertagi* and *Oesophagostomum radiatum* acquired up to 21 days after treatment and *Dictyocaulus viviparus* acquired up to 28 days after treatment.

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	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	22nd June 2011
Date product first authorised in the Reference Member State (MRP only)	21st January 2011
Concerned Member States (from September 2016)	Belgium, France, Germany, Italy, Portugal, Spain

I. SCIENTIFIC OVERVIEW

This was an application made in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC, for Topimec Plus 10/100 mg/ml Solution for Injection for Cattle. The reference product is Ivomec Super Injection for Cattle, licensed in the UK in August 1987. The recommended dose rate is 200 µg of ivermectin and 2 mg of clorsulon per kg bodyweight. This equates to 1 ml/50 kg bodyweight, administered by subcutaneous injection.

The product is intended for use in cattle to treat mixed infestations of adult liver fluke and gastro-intestinal roundworms, lungworms, eye worms, and/or mites and lice of beef and non-lactating dairy cattle. Gastro-intestinal roundworms targeted are as follows: *Ostertagia ostertagi* (including inhibited larval stages), *O. Lyrata, Haemonchus placei, Trichostrongylus axei, T. Colubriformis, Cooperia oncophora, C. punctata, C. pectinata, Bunostomum phlebotomum, Oesophagostamum radiatum, Strongyloides papillosus* (adult), *Nematodirus spathiger* (adult), *Nematodirus helventianus* (adult) and *Trichuris spp* (adult). Lungworms (adult and four-stage larvae): *Dictyocaulus viviparus*, liver fluke (adult): *Fasciola hepatica,* eye worms (adult)*: Thelazia spp,* warbles (parasitic stages): *Hyopderma bovis* and *Hyopderma lineatum,* mange mites: *Psoroptes bovis*, *Sarcoptes scabiei* var bovis, sucking lice: *Linognathus vituli, Haematopinus eurysternus* and *Solenoptes capillatus*.

The product may also be used to treat biting lice (*Damalina bovis*) and the mange mite *Chorioptes bovis,* however, complete elimination may not occur. A dose of 1 ml/50 kg bodyweight controls re-infection with *Haemonchus placei, Cooperia* spp. and *Trichostrongylus axei* acquired up to 14 days after treatment, *Ostertagia ostertagi* and *Oesophagostomum radiatum* acquired up to 21 days after treatment and *Dictyocaulus viviparous* acquired up to 28 days after

treatment. 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substances ivermectin and clorsulon, and the excipients glycerol formal, propylene glycol and monoethanolamine (for pH adjustment). The design of the product closely resembles that of the reference product, which overcomes the low aqueous solubility of the active substances. The absence of an anti-microbial preservative is justified by the non-aqueous nature of the product. The product is packed in translucent, high-density polyethylene containers of 50 ml, 250 ml and 500 ml. The containers are closed with siliconised bromobutyl rubber closures fastened with aluminium collars. The polyethylene containers are subjected to an infra-red identification test, and tests are performed on appearance, dimensions, mass and goodness of fit. Certificates from the supplier declare compliance with European and United States requirements for food and pharmaceutical use. The siliconised bromobutyl closures meet the Ph. Eur requirements for Type 1 rubber closures. The product is tested by infra-red spectroscopy, and for appearance dimensions and goodness of fit. The aluminium overseals are tested for appearance, dimensions and goodness of fit. The particulars of the containers and controls performed are provided and conform to the regulation.

The absence of preservative 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

Glycerol formal and propylene glycol are mixed, followed by the addition of ivermectin and clorsulon. The batch is made up to quantity with propylene glycol and mixed again. The solution is then filter-sterilised before being aseptically poured into containers. 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.

[1] SPC – Summary of Product Characteristics.

C. Control of Starting Materials

The active substances are clorsulon and ivermectin, established active substances established substance described in the European Pharmacopoeia, (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice.

Active substance 1

Certificates of Suitability for ivermectin were provided, and the active substance complies with a monograph in the Ph. Eur. Batch analysis was provided for three batches of the active substance. For supplier validation, three batches are tested against the requirements of the specification. Following this, each delivery is checked for compliance with solubility and identity tests and description. One batch annually is fully tested.

Active substance 2

In the absence of a Ph. Eur monograph for clorsulon, the specification is based on the monograph in the United Sates Pharmacopoeia. Additional tests are performed for microbial purity, limiting total aerobic count to nmt[2] 103 cfu/g and total mould and yeast count to 102 cfu/g. Batch analysis was provided on three batches of clorsulon, demonstrating compliance with the current specification.

The active substance specifications are 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

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

Not applicable.

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 sites have been provided demonstrating compliance with the specification. In-process controls include a visual check on solution at various points during the manufacturing procedure, fill volume and assembled pack appearance. Two batches of

[2] nmt – not more than.

finished product were examined for homogeneity and compliance with specification. These were satisfactory.

G. Stability

Active substances

A Certificate of Suitability for ivermectin was submitted, highlighting a retest interval of three years for material stored in a double-lined, heat-sealed polyethylene bag within an aluminium tin. For clorsulon, data showed that the active substance was stable when stored for three years under long-term conditions.

Finished Product

Two batches of product, stored in the proposed packaging at 25°C/60%RH and 40°C/75%RH, for thirty-six months provided acceptable stability data. An indication that ivermectin was somewhat sensitive to light means that a direction is included in the product literature to protect the product from light and store in the outer carton. Freeze-thaw cycling had no effect on the product.

In-Use

Data were presented on one batch of product in the 50 ml pack, stored for twelve months, and on two 500 ml packs. No adverse events were detected in respect to any parameter tested within the specifications. The shelf life of the product as packaged for sale was therefore determined to be three years, and on first opening of the immediate packaging, the product must be used within twenty-eight days. Any unused material should be discarded. The product should be kept within the outer carton to protect it from light.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening the immediate packaging: 28 days.
This veterinary medicinal product does not require any special temperature storage.
Keep the container in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, there was no requirement for pharmacological, or toxicological data in this section. A bioequivalence study using Ivomec Super Injection for Cattle as the reference product and Topimec Plus 10/100 mg/ml Solution for Injection for Cattle as the test substance was submitted. This data is presented in Part IV.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

User Safety

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

The product is safe for use when used as described in the SPC. The following warnings are specified:-

- Do not smoke, eat or drink whilst handling the product.
- Wash hands after use.
- Direct contact with the skin should be avoided.
- Wear gloves and glasses when handling the veterinary medicinal product.
- Take care to avoid self-injection: the product may cause local irritation and/or pain at the injection site.
- In case of accidental self injection, seek medical advice and show the label to the doctor.

Ecotoxicity

The environmental safety data originated in part from data provided for Animec Super Solution for Injection for Cattle. The environmental risk assessment (ERA) for Topimec Plus 10/100 mg/ml Solution for Injection for Cattle states that the likely treatment scenario for the product will be when a simultaneous fluke/gastrointestinal nematode treatment or fluke/lice treatment is required. A Phase II assessment was required for this product, as it is a parasiticide used in pasture animals.

A Phase II risk assessment was carried out on ivermectin and clorsulon. All information for ivermectin was sourced from data within the public domain. Data were provided on the metabolism and excretion of the active substance, on fate in the environment and on the effects on non-target organisms. PEC^{3}_{soil}, $PEC_{groundwater}$, $PEC_{surfacewater}$, $PEC_{sediment}$ and PEC_{dung} values were calculated using

[3] PEC – Predicted Environmental Concentration.

methods described in the CVMP guideline, using the appropriate VICH equations 1 and 2. Sufficient data were provided.

For clorsulon, a description of the metabolism and excretion of the active substance was provided, in addition to data relating to fate in the environment. 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

Bioequivalence with the reference product was demonstrated. An Article 35 referral procedure was completed by the CVMP[4] (EMEA/V/A/027) in relation to the withdrawal period for ivermectin and ivermectin/clorsulon injectables for cattle, and a sixty-six day withdrawal period was approved. No further depletion studies were therefore required.

MRLs

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Ivermectin	22,23-Dihydroavermectin B1a	All food producing species	100 µg/kg 30 µg/kg 100 µg/kg	Liver Kidney Fat	Not for use in animals producing milk for human consumption
Clorsulon	Clorsulon	Bovine	200 µg/kg 100 µg/kg 35 µg/kg	Kidney Liver Muscle	

Withdrawal Periods

Based on the data provided above, a withdrawal period of 66 days for meat and offal is justified. The product is not for use in non-lactating dairy cows including pregnant heifers within 60 days of calving.

[4] CVMP – The Committee for Medicinal Products for Veterinary Use.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

No data were submitted under this section. The applicant cited the pharmacodynamic data for the reference product. Ivermectin and clorsulon have been extensively investigated with regard to pharamcodynamic properties, and used in a number of similar products.

Pharmacokinetics

Pharmacokinetic tests were not required for this generic application, however, the applicant provided data on a single dose, randomised, positive-controlled, cross-over bioequivalence study with an ivermectin/clorsulon injectable formulation in cattle.

Topimec Plus 10/100 mg/ml Solution for Injection for Cattle was compared with the reference product, Ivomec Super Injection for Cattle. A suitable number of cattle were divided into groups. After acclimatisation, weighing and blood sampling, the animals were divided into two groups. A single subcutaneous injection of 0.2 mg/kg ivermectin and 2 mg/kg clorsulon of either reference product or test product was administered. After a 57 day wash-out period, the second phase of the study took place, with animals being given the reciprocal product. Blood sampling and physiological parameters were analysed at various time points. Ivermectin and clorsulon levels were measured and compared using appropriate HPLC methods.

Primary parameters used for statistical analysis were AUC_t[5] and C_{max}[6]. Bioequivalence was claimed if the 90% confidence interval for both AUC_t and C_{max} were contained within 80%-125% confidence limits. The significance level was deemed to be ($p < 0.05$).

No adverse reactions were seen during the study. The test product was demonstrated to be bioequivalent to the reference product.

[5] AUC_t - Area under the plasma concentration-time curve from time zero to time t.
[6] C_{max} – Maximum (peak) plasma drug concentration.

Tolerance in the Target Species of Animals

No data were required for tolerance in the target species, as bioequivalence was demonstrated with the reference product. However, the applicant conducted overdose and repeat dose safety studies in the target species, the results were satisfactory. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

There was no requirement to provide data in this section, as bioequivalence was demonstrated with the reference product. Contraindications and warning for Topimec Plus 10/100 mg/ml Solution for Injection for Cattle are the same as those of the reference product. Additional warnings were added as appropriate:-

Section 4.2 The indication now provides data on mixed infestations. Section 4.9 now includes the text 'The timing for treatment should be based on epidemiological factors and should be customised for each individual farm. A dosing programme should be established by the surgeon.' The product is not indicated for us in cattle producing milk for human consumption. The SPC refers to the contraindication for use in other species, with Section 4.3 referring specifically to a risk of fatality in dogs. Section 4.4 now reflects warnings related to anthelmintic resistance, and the SPC also contains statements relating to local tolerance. The SPC was also updated to highlight clinical signs, duration and nature of overdose/toxicity syndromes and available symptomatic treatment.

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)