ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Virbamec Pour-On Solution for Cattle 5 mg/ml

PuAR correct as of 24/07/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0153/001/E002
Name, strength and pharmaceutical form	Virbamec Pour-On Solution for Cattle 5 mg/ml
Applicant	Virbac S.A. 1ère avenue, 2065m - LID 06516 Carros Cedex France
Active substance(s)	Ivermectin
ATC Vetcode	QP54AA01
Target species	Cattle
Indication for use	Virbamec Pour-On is indicated for the treatment of gastro-intestinal nematodes, lungworms, warbles, chorioptic and sarcoptic mange mites, sucking and biting lice of beef and non-lactating dairy cattle. <u>Gastro-intestinal roundworms (adults and 4th stage larvae):</u> *Ostertagia ostertagi* (L4, adults and inhibited stages) *Haemonchus placei* (L4, adults) *Trichostrongylus axei* (L4, adults) *Trichostrongylus colubriformis* (L4, adults) *Cooperia spp*. (adults) *Cooperia puntacta* (adults) *Cooperia oncophora* (adults) *Oesophagostomum radiatum* (L4, adults) *Strongyloides papillosus* (adults) *Trichuris spp*. (adults) <u>Lungworms (adults and 4th stage larvae):</u> *Dictyocaulus viviparus* <u>Warbles (parasitic stages):</u> *Hypoderma bovis* *Hypoderma lineatum*

	Mites: *Sarcoptes scabiei var bovis* *Chorioptes bovis* Lice: Sucking lice *Linognathus vituli* *Haematopinus eurysternus* Biting lice *Damalinia bovis* Virbamec Pour-On, at the recommended use level of 500 mcg ivermectin per kg bodyweight, has a persistent activity on: *Dictyocaulus viviparus:* for up to 28 days *Ostertagia spp:* for up to 21 days *Oesophagostomum radiatum:* for up to 21 days *Cooperia spp.:* for up to 14 days *Trichostrongylus axei:* for up to 14 days Virbamec Pour-On helps in the control of the mange mite *Chorioptes bovis* but complete elimination may not occur. Virbamec Pour-On has also a persistent activity on the horn Fly (*Haematobia irritans)* for 28 days, partial efficacy may last for up to 35 days post application. Occasionally variable activity may be observed against *Haemonchus placei* (L4), *Cooperia spp*, *Trichostrongylus axei* and *Trichostrongylus colubriformis.* To obtain optimal benefit of Virbamec Pour-On, the product is recommended to be used as part of treatment programs, based on the epidemiology of the parasites in question.

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	Application in accordance with Article 32 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	23 February 2005
Date product first authorised in the Reference Member State (MRP only)	12 January 2001
Concerned Member States for original procedure	Austria Belgium Denmark France Germany Ireland Luxembourg Portugal Spain Sweden

I. SCIENTIFIC OVERVIEW

Virbamec pour-on solution for cattle 5 mg/ml is authorised for use in cattle for the treatment of gastro-intestinal nematodes, lungworms, warbles, chorioptic and sarcoptic mange mites, sucking and biting lice of beef and non-lactating dairy cattle as follows: Gastrointestinal roundworms (adult and fourth larval stages*), Ostertagia ostertagi* (fourth larval stages, adults and inhibited stages), *Haemonchus placei (*fourth larval stages and adults), *Trichostrongylus axei (*fourth larval stages and adults), *Trichostrongylus colubriformis* (fourth larval stages and adults*), Cooperia Spp.* (adults), *Cooperia punctata* (adults*)*, *Cooperia oncophora* (adults), *Oesophagostomum radiatum (*fourth larval stages and adults), *Strongyloides papillosus* (adult), *Trichuris* spp (adult). Treatment of lungworms (adult and fourth-stage larvae) *Dictylocaulus viviparous*; treatment of warbles (parasitic stages) *Hypoderma bovis, Hypoderma lineatum*; treatment of mites *Sarcoptes scabiei var bovis, Chorioptes bovis*, treatment of sucking lice (*Linognathus vituli* and *Haematopinus eurysternus*) and biting lice *(Damalinia bovis*).

Virbamec pour-on solution for catlle 5 mg/ml, at the recommended use level of 500 mcg ivermectin per kg bodyweight, has a persistent activity on *Dictyocaulus viviparous* for up to 28 days, on *Ostertagia spp* for up to 21 days, on O*esophagostomum radiatum* for up to 21 days, on C*ooperia spp.* for up to 14 days and on *Trichostrongylus axei* for up to 14 days.

Virbamec pour-on solution for cattle 5 mg/ml helps in the control of the mange mite *Chorioptes bovis* but complete elimination may not occur. The product also has a persistent activity on the horn fly (*Haematobia irritans)* for 28 days, partial efficacy may last for up to 35 days post application. Occasionally variable activity may be observed against *Haemonchus placei* (L4), *Cooperia spp*, *Trichostrongylus axei* and *Trichostrongylus colubriformis.*

To obtain optimal benefit, the product is recommended to be used as part of treatment programs, based on the epidemiology of the parasites in question.

This application was submitted under the Mutual Recognition Repeat Use Procedure in accordance with Article 32 of Directive 2001/82/EC as amended. The original application was made in the UK in accordance with Article 13 (1) (a) (iii) of Directive 2001/82/EC and a Marketing Authorisation was granted on 12 January 2001. The applicant had claimed essential similarity between Virbamec pour-on solution for cattle 5 mg/ml and Ivomec pour-on for cattle marketed by Merial.
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 and the slight reactions observed are indicated in the SPC[1]. The product is safe for the user, for the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated

[1] Summary of Product Characteristics

in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC.

II. QUALITY ASPECTS

A. Composition

The active substance in Virbamec pour-on solution for cattle 5 mg/ml is ivermectin 5 mg/ml, and the excipients are crodamol CAP or cetearyl ethylhexanoate and isopropylmyristate, triethanolamine and isopropyl alcohol.

The containers for Virbamec pour-on solution for cattle 5 mg/ml are composed of high density polyethylene with low density polyethylene seal closure fitted with a child resistant screw cap. The containers are of a 500 ml, 1000 ml or 2.5 l size.

The choice of formulation is justified.

The product is an established pharmaceutical form and its development has been 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. The applicant has provided details of the stages of, and method of manufacture. In-process controls have also been described. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance ivermectin is the subject of a monograph in the Ph. Eur.[2]. The supporting data have been provided in the form of EDQM[3]. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

The excipients are crodamol CAP or cetearyl ethylhexanoate and isopropylmyristate, triethanolamine and isopropyl alcohol.

For isopropyl alcohol, a Ph. Eur monograph exists and the British Pharmacopoeial monograph is used for triethanolamine. Crodamol CAP or cetearyl ethylhexanoate and isopropylmyristate do not have a pharmacopoeial monograph, an in-house specification was developed for this excipient.

[2] European Pharmacopoeia
[3] European Directorate for the Quality of Medicines and Healthcare

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. The satisfactory validation data for the analytical methods have been provided.

G. Stability

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. The shelf life of 2 years is justified when stored under appropriate conditions.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after opening the immediate packaging: 6 months.

Special precautions for storage
Highly flammable - Do not smoke. Keep away from heat, sparks, open flames or other sources of ignition.
Store the product in the original container and keep tightly closed.
Keep the container in the outer carton in order to protect from light.
The container should be stored in an upright position.
If stored at low temperatures below 0°C, Virbamec pour-on may appear cloudy. Allowing to warm at room temperature will restore the normal appearance without affecting efficacy.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacological data were not required for this generic application. However, the applicant submitted published literature and an *in vivo* bioequivalence study in cattle. These are discussed below in section IV.

Toxicological Studies

Since this generic application was submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on toxicology were not required.

User Safety

The following warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Virbamec pour-on solution for cattle 5 mg/ml may be irritating to human skin and eyes and the user should be careful not to apply it to himself or other persons.
- Operators should wear nitrile rubber gloves, rubber boots and a waterproof coat when applying the product. Protective clothing should be washed after use.
- If accidental skin contact occurs, wash the affected area immediately with soap and water. If accidental eye exposure occurs, flush the eyes immediately with water and get medical attention.
- Do not smoke or eat while handling the product.
- Wash hands after use.
- Use only in well ventilated areas or outdoors.
- HIGHLY FLAMMABLE.

Ecotoxicity

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 the product is administered by the same route and at the same dosage rate as the reference product and was demonstrated to be essentially similar.

MRLs

The MRLs for ivermectin in cattle are in Annex I of Council Regulation 2377/90 as follows:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissue
Ivermectin	22,23-dihydroavermectin B1a	Bovine	100 ug/kg 40 ug/kg	Liver Fat

Withdrawal Periods

Meat and offal: 28 days
Milk:
Not permitted for use in lactating cows producing milk for human consumption. Do not use in pregnant cows, which are intended to produce milk for human consumption, within 60 days of expected parturition.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics:
No data were submitted for this section. Ivermectin has been extensively investigated with regard to pharamcodynamic properties, and used in a number of similar products. This is considered acceptable.

Pharmacokinetics:
The applicant provided published references and conducted an *in vivo* bioequivalence study. The aim of the study was to determine bioequivalence of the Virbamec pour-on solution for cattle 5 mg/ml and Ivomec pour-on for cattle when applied topically at the recommended dose rate of 500 µg/kg body weight in cattle. A suitable number of cattle were divided into groups. Both products were applied, using 50 ml plastic disposable syringes, along the dorsal midline of the animal from the withers to the base of the tail. The application rate was 1.0 ml per 10 kg bodyweight (500 µg ivermectin per kg). Pharmacokinetic parameters were evaluated by analysis of the ivermectin content of blood plasma. Primary parameters used for statistical analysis were AUC_t[4] and C_{max}[5]. No adverse reactions were seen during the study. The test product was demonstrated to be bioequivalent to the reference product.

Tolerance in the Target Species of Animals

No data were required for this section as bioequivalence was demonstrated with the reference product.

Resistance

Not applicable.

IV.B Clinical Studies

No data were required for this section. However, the applicant submitted two studies. The aim of the first study was to confirm that rainfall immediately prior to and up to 24 hours after treatment didn't have a negative impact on the efficacy of the formulation against mixed gastrointestinal nematode infestations in cattle. This study was well designed and concluded that Virbamec pour-on solution for cattle 5mg/ml had 100% efficacy against mixed gastrointestinal nematode infestations. The second study was conducted to evaluate the therapeutic efficacy of 5 mg/ml ivermectin pour-on formulations against a range of cattle nematodes. This study concluded that Virbamec pour-on solution for

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

cattle 5 mg/ml is highly effective against the parasites and equally effective as the reference product.

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)