ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Virbamec Super 10 mg/ml, 100 mg/ml Solution for Injection

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Virbamec Super 10 mg/ml, 100 mg/ml Solution for Injection
Applicant	Virbac S.A. 1ère avenue 2065 m L.I.D. 06516 Carros Cedex France
Active substance(s)	Ivermectin, Clorsulon
ATC Vetcode	QP54AA51
Target species	Cattle
Indication for use	For the treatment of mixed trematode and nematode or arthropod infestations, due to adult and immature roundworms, lungworms, warbles, mites, lice and liver fluke in cattle. Gastro-intestinal roundworms (adult and fourth-stage larvae): *Ostertagia ostertagi* (including inhibited larval stages) *O. lyrata* *Haemonchus placei* *Trichostrongylus axei* *Trichostrongylus colubriformis* *Cooperia oncophora* *Cooperia punctata* *Cooperia pectinata* *Bunostomum phlebotomum* *Oesophagostomum radiatum* *Strongyloides papillosus* (adult) *Nematodirus helvetianus* (adult) *Nematodirus spathiger* (adult) Lungworms (adult and fourth-stage larvae): *Dictyocaulus viviparus* Liver fluke (adult):

	Fasciola hepatica Warbles (parasitic stages): *Hypoderma bovis* *Hypoderma lineatum* Mange mites: *Psoroptes bovis* *Sarcoptes scabiei* var. *bovis* Sucking lice: *Linognathus vituli* *Haematopinus eurysternus* The product may also be used as an aid in the control of the mange mite *Chorioptes bovis*, but complete elimination may not occur.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

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.

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, according to Article 13 (1) of Directive 2001/82/EC as amended. The reference product was Ivomec Super Injection for Cattle, first authorised in the UK in August 1987. The reference product used in the bioequivalence study was Ivomec D Bovin Solution Injectable, authorised in France.

The product is indicated for use in treating mixed trematode and nematode or arthropod infestations, as follows: Gastro-intestinal roundworms (adult and fourth-stage larvae): *Ostertagia ostertagi* (including inhibited larval stages), *O. Lyrata, Haemonchus placei, Trichostrongylus axei, Trichostrongylus colubriformis, Cooperia oncophora, Cooperia punctata, Cooperia pectinata, Bunostomum phlebotomum, Oesophagostomum radiatum, Strongyloides papillosus* (adult), *Nematodirus helvetianus* (adult), *Nematodirus spathiger* (adult). Lungworms (adult and fourth-stage larvae): *Dictyocaulus viviparus.* Liver fluke (adult): *Fasciola hepatica.* Warbles (parasitic stages): *Hypoderma bovis, Hypoderma lineatum.* Mange mites: *Psoroptes bovis, Sarcoptes scabiei* var. *bovis.* Sucking lice: *Linognathus vituli, Haematopinus eurysternus.*

The product may also be used as an aid in the control of the mange mite *Chorioptes bovis*, but complete elimination may not occur. It may not be used for non-lactating dairy cows including pregnant heifers within 60 days of calving, and is not to be used in any other species. Severe adverse reactions may occur, including fatalities, in dogs for example.

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.

[1] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains clorsulon and ivermectin as active substances and excipients propyl gallate (E310), disodium, edetate, glycerol formal, propylene glycol and water for injections. The container/closure system consists of 50 ml, 200 ml, 500 ml or 100 ml colourless LDPE vials with chlorobutyl rubber stoppers and aluminium overseals. The particulars of the containers and controls performed are provided and conform to the regulation. The absence of preservative was justified. Both reference product and generic product contain 1 g ivermectin and 10 g clorsulon per 100 ml of solution. The excipient formulations of both product and reference product are similar, and the formulation was permitted as an 'essential similarity' application.

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. Two excipients are mixed, a proportion of which is used to dissolve the clorsulon. Into the remainder, the other excipients are added, along with ivermectin. After pooling, the product is filtered and sterilised before being poured into vials.

C. Control of Starting Materials

The active substances are clorsulon and ivermectin, established active substances. Ivermectin is monographed in the European Pharmacopoeia (Ph. Eur), while clorsulon is controlled by monographs in the United States 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.

Excipients described in the Ph. Eur are disodium edetate, propyl gallate, water for injections and nitrogen used during manufacture. Glycerol formal is not described in a pharmacopoeia, an in-house specification was 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 site have been provided demonstrating compliance with the specification. Tests include those for: appearance, identification of the active substances and excipients, and sterility.

G. Stability

Stability data on the active substances 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 were provided, and shown to be appropriate. Three batches of product were examined under VICH[2] conditions. Two batches of product were examined for in-use stability.

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.
- Protect from light.
- Store in the original container.
- Following withdrawal of the first dose, use the product within 28 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological data were not required.

[2] VICH – International Cooperation on Harmonisation of Technical Requirements for Veterinary Medicinal Products.

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, when used as directed.

III.A Safety Testing

User Safety

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

- Do not smoke, drink or eat while handling the product.
- Wash hands after use.
- Avoid contact with skin and eyes.
- Take care to avoid self-administration, the product may cause irritation and/or pain at the site of injection.

Ecotoxicity

The applicant provided first and second phase environmental risk assessments in compliance with the relevant guideline. The risk assessments were carried out on ivermectin and clorsulon individually, and then in combination.

Clorsulon

Shown to be moderately persistent and mobile in soil, PNEC[3] values were determined for algae, fish, daphnia, earthworms, dung fly and dung beetle larvae. Comparision of PNECS with worst case scenario PEC[4] values provide a risk quotient of <1.

Ivermectin

Persistent but non-mobile in soil, PNEC values were determined for earthworms, algae, soil, micro-organisms, daphnia, fish, sediment organisms, dung fly and dung beetle larvae. All PEC values were acceptable, but it was not possible to exclude a risk for aquatic organisms.

A suitable warning appears on the SPC and product literature: Ivermectin is highly toxic to aquatic invertebrates. Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment to avoid adverse effects on aquatic organisms. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[3] PNEC – Predicted No Effect Concentration.
[4] PEC – Predicted Environmental Concentration.

III.B Residues documentation

Residue Studies

Residue depletion studies were completed by the applicant which showed bioequivalence with the reference product for clorsulon, but not for ivermectin. However, an Article 35 CVMP[5] referral procedure was completed, regarding the withdrawal period for clorsulon/ivermectin-containing for cattle, and the withdrawal period for cattle meat was agreed as 66 days. The stipulation for milk withdrawal for this product was agreed as follows: do not use in animals producing milk for human consumption. Do not use in non-lactating dairy cows including pregnant heifers within 60 days of calving.

MRLs

MRL[6]s for ivermectin and clorsulon in cattle are listed in an Annex of Council Regulation 2377/90.

MRLs are listed below: /kg

	MRLs	Residue Marker
Ivermectin		
Liver	100 µg	22,23-Dihydroavermectin
Fat	100 µg	
Kidney	30 µg	
Clorsulon		
Liver	35 µg	Clorsulon
Fat	100 µg	
Kidney	200 µg	

Withdrawal Periods

Based on the data provided above, and on the CVMP referral, a withdrawal period of 66 days for meat in cattle was approved. For milk, do not use in animals producing milk for human consumption. Do not use in non-lactating dairy cows including pregnant heifers within 60 days of calving.

[5] CVMP – Committee for Veterinary Medicinal Products for Veterinary Use.
[6] MRL – Maximum Residue Limit.

IV CLINICAL ASSESSMENT (EFFICACY)

Pharmacological tests are not required for applications where 'essential similarity' is claimed. The applicant nevertheless supplied appropriate references, in addition to a bioequivalence study, performed in order to compare reference and generic products.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Ivermectin is a member of the macrolide (avermectin) family of compounds. These active substances act against both arthropod and nematode parasites, ivermectin binding with high affinity to glutamate-gated chloride channels of the target parasite. Hyperpolarisation ensues, causing interference to the neural stimuli of muscles. Another action of avermectins is the putative potentiation of GABA[7]-gated chloride channels. The effect is not seen in mammals, as the macrocyclic lactones do not readily cross the blood-brain barrier. Ivermectin has no effect on tapeworms and liver fluke, likely because of the difference in neuronal structure.

Clorsulon is a member of the benzenesulphonamide family, a competitive inhibitor of enzymes involved in the oxidation of glucose, depriving the liver fluke of metabolic energy.

Pharmacokinetics

Ivermectin has a very short distributive phase following intravenous administration, being deposited in body fat. There is a large volume of distribution, at 1.9 L/kg, with a half-life of 2.8 days. For clorsulon, after administration by the subcutaneous route C_{max}[8] was obtained in one study after 6 hours. Clorsulon binds extensively to plasma proteins and also to carbonic anhydrase in erythrocytes, prolonging the drug in the circulation.

When clorsulon and ivermectin were delivered at 200 µg/kg ivermectin and 2 mg/kg clorsulon, (as described for the reference product), the combination of active substances was efficacious against *Fasciola hepatica*. It was concluded that for this application, as seen previously, there are no adverse interactions between the two active substances.

A bioequivalence study was included with this application, however, the results were not a requirement for this type of application, where justification for the combination has already been accepted in the European Union.

[7] GABA – Gaba-aminobutyric acid.
[8] C_{max} – Maximum plasma concentration.

Bioequivalence study

The reference product and generic product were compared in a GLP[9]-compliant single dose, randomised, parallel design study, containing a suitable number of cattle. During acclimatisation, cattle were treated with endo- and ecto-parasiticides before being divided into groups, (tilmicosin was also administered at 10 mg/kg as some animals presented with cough and fever). The test and reference products were then given to either group of cattle, at 200 µg/kg bodyweight ivermectin and 2 mg/kg bodyweight of clorsulon, by subcutaneous injection in the neck. Observations were performed at various time points, and blood samples analysed. Statistical analysis was as defined in the CVMP guideline for equivalence studies. No adverse reactions due to the products were observed during the study.

Tolerance in the Target Species of Animals

Although tolerance studies were not required for this type of application, as 'essential similarity' was demonstrated, the applicant included bibliographical references, and included the data generated from a bioequivalence study, (see above). The bioequivalence study provided data in support of the local tolerance of the product. A withdrawal period study provided useful information on the local tolerance of the product.

IV.B Clinical Studies

The results of clinical studies are not a requirement for this type of application.

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.

[9] GLP – Good Laboratory Practice.

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)