IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Endectomectin 5 mg/ml Pour-On Solution

Introduction

Name, strength and pharmaceutical form	Endectomectin 5 mg/ml Pour-On Solution
Active substance(s)	Ivermectin
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP Northern Ireland
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended
Date of Authorisation	2nd February 2007
Target species	Cattle
Indication for use	For the treatment of internal and external parasites of cattle (as listed in SPC)
ATCvet code	QP54AA01 Ivermectin

PRODUCT SUMMARY

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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

II QUALITY ASPECTS

The product contains 5 mg/ml ivermectin as the active substance and the excipients crodamol CAP, trolamine, isopropyl alcohol and patent blue V dye.

The container/closure system consists of single-neck, twin-neck or squeeze-measure high density polyethylene dispensers of 250 ml and 1.0 L and low density polyethylene backpacks of 2.5 L and 5 L.

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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is ivermectin, an established substance described in the European Pharmacopoeia. 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 has been provided.

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.

D. Control on Intermediate Products

Not applicable.

E. 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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. ***Other Information***

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

This is a generic application based on the reference product Ivomec Pour-on (Merial), which has the same qualitative and quantitative composition in terms of active substance, and has the same pharmaceutical form. Bioequivalence of the two products has been demonstrated, therefore similar safety can be assumed.

Pharmacological Studies

Pharmacodynamics:
Ivermectin is a member of the macrocyclic lactone class of endectocides which bind to glutamate-gated chloride ion channels, which occur in invertebrate nerve and muscle cells. This results in paralysis and death of the parasite. Compounds of this class may also interact with chloride channels gated by the neurotransmitter gamma-aminobutyric acid (GABA).

Pharmacokinetics:
The applicant carried out a Good Laboratory Practice (GLP) compliant study to compare the pharmacokinetics of Ivermectin following administration of Endectomectin Pour-On and the reference product Ivomec Pour-On (Merial). The confidence intervals for the pivotal pharmacokinetic parameters (Cmax and AUC) are within the allowable range for bioequivalence as defined in the current Bioequivalence Guideline.

Toxicological Studies

As this is an application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required

Other Studies

As this is an application according to Article 13, and bioequivalence with a reference product has been demonstrated, further studies are not required

Studies on Metabolites, Impurities, Other Substances and Formulation:
As this is an application according to Article 13, and bioequivalence with a reference product has been demonstrated, information on metabolites is not required. Impurities are listed and are as detailed in the European Pharmacopoeia pre-publication monograph. A description of each excipient is provided, with supportive product information. The excipients are commonly used in topical veterinary /human pharmaceuticals, cosmetics and/or foodstuffs

User Safety

The applicant has provided a user safety assessment. Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety to users of the product.

Environmental Risk Assessment

As this is an application according to Article 13, and bioequivalence with a reference product has been demonstrated, an ecotoxicity assessment is not required. Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues Documentation

The product is intended for use in cattle which are not producing milk for human consumption. It contains 0.5% w/v Ivermectin and is to be administered by pour-on as a single dose of 500 microgram Ivermectin per kg.

Residue Studies

The applicant has conducted GLP compliant residue depletion studies which show that concentrations of Ivermectin in all tissues examined (liver, fat, kidney, muscle from application site) were well below the relevant maximum residue limits (MRL) from 21 days after administration.

MRLs

Ivermectin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All mammalian food species
Muscle	30 µg/kg
Liver	100 µg/kg
Kidney	30 µg/kg
Fat	100 µg/kg

Withdrawal Periods

Based on the data provided above, the withdrawal period of 28 days for meat and offal is justified. It includes a safety span of 33% and corresponds to that of the reference product, Ivomec Pour-On, to which bioequivalence has been demonstrated. The product is not permitted for use in lactating cows producing milk for human consumption. It is not to be used in non-lactating dairy cows including pregnant heifers within 60 days prior to calving.

Analytical Methods used

The Ivermectin H2B1a content was measured using an HPLC method which was fully validated.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

This is a generic application based on the reference product Ivomec Pour-on (Merial), which has the same qualitative and quantitative composition in terms of active substance, and has the same pharmaceutical form. Bioequivalence of the two products has been demonstrated, therefore similar efficacy can be assumed.

Tolerance in the Target Species of Animals

The applicant conducted a GLP compliant, controlled target animal tolerance study using multiples of the recommended dose in cattle. All doses were administered topically on one occasion to 2 sites on dorsal midline. Parameters evaluated included haematology and biochemistry as well as physical examination and post mortem examination of the application site.

No significant adverse effects were seen following the administration of doses up to twice the recommended dose.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

As this is an application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims are the same as those for the reference product.

V OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

This is a generic application based on the reference product Ivomec Pour-on (Merial), which has the same qualitative and quantitative composition in terms of active substances, and has the same pharmaceutical form. Bioequivalence of the two products has been demonstrated in a GLP compliant pharmacokinetic study, within the allowable limits as defined in the current CVMP Bioequivalence Guideline. Information relating to the excipients has been provided and is sufficient to assure user safety. No environmental risk assessment is required as this is a generic application. Residue depletion studies have been conducted which confirm that the 28 day withdrawal period which applies to the reference product is adequate for Endectomectin Pour-On.

In conclusion, a similar profile to the reference product with respect to safety to human and environmental safety can be assumed.

A GLP compliant target animal safety study, using twice the recommended dose, has shown that the product is well tolerated in cattle at twice the recommended dose. The efficacy claims are identical to those for the reference product in the RMS.

Ivermectin is a well established substance which has been used in veterinary medicines in the EU for many years. There are no issues which would raise any concerns regarding use of Endectomectin Pour-On for the treatment of cattle. The risk benefit assessment is positive.

VI 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 HPRA website.

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.

Changes:

None.