IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Macromectin 0.8 mg/ml oral solution for sheep

PRODUCT SUMMARY

EU Procedure number	IE/V/0179/001
Name, strength and pharmaceutical form	Macromectin 0.8 mg/ml oral solution for sheep
Active substance	Ivermectin
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Bibliographical, according to Article 13.aof Directive 2001/82/EC as amended
Date of Authorisation	02 September 2005
Target species	Sheep
Indication for use	Endectocide
ATCvet code	QP54AA01
Concerned Member States	IT & SE

PUBLIC ASSESSMENT REPORT

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

Ivermectin is a well established substance which has been used in veterinary medicines in the EU for well in excess of the 10 years required for this type of application.The applicant has provided sufficient bibliographical information to confirm well established use of ivermectin in sheep at the same dose and pharmaceutical form as proposed for this product

This section reflects the initial scientific discussion on the approval of Macromectin Drench. Please refer to section V for significant post-approval changes which are important for the quality, safety and efficacy of the product.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

Composition of the Veterinary Medicinal Product

Active substance
Ivermectin

Excipients
Tween 80
N,N-dimethylacetamide
Benzyl Alcohol

Disodium Hydrogen Orthophosphate Dihydrate
Sodium Dihydrogen Orthophosphate Dihydrate
Purified Water

Container/Closure System
Paramectin Drench is supplied in 1.0 L, 2.5 L and 5.0 L and 2 x 5 L high density polyethylene Jerrycan containers complete with polypropylene caps and 1.0 L, 2.5 L, 5.0 L and 2 x 5.0 L high density polyethylene Back-pack containers complete with polypropylene plastic screw caps.

Development Pharmaceutics
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

B.1 Manufacturing Formula
This information is commercially confidential.

B.2 Method of Preparation
The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

B.3 Validation of the Manufacturing Process
The product is manufactured using conventional manufacturing techniques.

C. Control of Starting Materials

C.1 Active Substance
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 applicant has provided a specification which ensures that that the substance is suitably controlled by the monograph for ivermectin.

Batch analytical data demonstrating compliance with this specification have been provided.

C.2 Other Substances
Other substances in the product comply with the European Pharmacopoeia.

C.3 Packaging Materials
The product is packaged in high density polyethylene Jerrycan and back-pack containers. The packaging materials comply with relevant EU standards.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances of ruminant animal origin 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 have been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

F.1 Stability Studies on the Active Substance

A suitable retest period for the active substance has been assigned based on the data provided.

F.2 Stability Tests on the Finished Product

Stability data on the 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.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Precise Identification of the Product concerned by the Application

The product is an oral solution containing 0.08%w/v ivermectin.

III.A Safety Testing

Pharmacological Studies
Pharmacodynamics:

The applicant has provided bibliographical data which show that ivermectin is the 22,23-dihydro derivative of avermectin B1a and B1b. Avermectins have parasiticidal activity.They interact with glutamate-gated chloride ion channels in nematode parasites, to increase membrane permeability to chloride ions, causing paralysis and death of the parasite.

Pharmacokinetics:

The applicant has provided bibliographical data describing the characteristics of ivermectin.The applicant has also conducted a pharmacokinetic study using Macromectin Drench which shows that the product is bioequivalent with Oramec Drench (Merial), a version of the pioneer product mentioned in much of the bibliography. This confirms that the bibliography is relevant to Paramectin Drench.

Toxicological Studies
The applicant has provided bibliographical data which show that ivermectin has as a good margin of safety in a variety of species. Ivermectin has low toxicity in mammals even at high doses, probably because of its limited ability to cross the blood-brain barrier. Toxic signs are mainly CNS related e.g mydriasis, ataxia, tremor.Collie dogs are more sensitive than other breeds.In pregnant animals, effects on the foetus only occur at very high doses.Ivermectin is not mutagenic or carcinogenic.

Other Studies
There are numerous reports of the safe use of ivermectin in humans, particularly for the treatment of onchocerciasis, usually at an intermittent oral dose of 200microgram/kg. Any major side effects are attributed to the death of the microfilarial parasites rather than to the drug itself.
Excipients are commonly used in veterinary and human products for oral administration.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that significant exposure is unlikely provided the product is used as intended. Accidental ingestion of a small volume is likely to involve doses well below the usual human dose and would not be expected to cause adverse effects.

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

Environmental Risk Assessment
Ivermectin is known to pose environmental hazards to fish and aquatic life. Warnings regarding disposal on the product literature correspond to those of other oral products containing ivermectin and are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues Documentation
Precise Identification of the Product concerned by the Application
The product is intended for use in sheep.It contains 0.8 mg ivermectin per ml and is to be administered orally as a single dose.

Residue Studies
Residue depletion studies using the final formulation have been conducted in sheep. Results show that residues depleted to well below the MRL in all tissues before the end of the withdrawal period

MRLs
Ivermectin is listed in Annex I of Council Regulation 2377/90.The marker substance is 22,23 dihydroavermectin H2B1a.

MRLs are listed below:

	All mammalian species (microgram/kg)
Liver	100
Fat	100
Kidney	30

Withdrawal Periods
Based on the data provided above, a withdrawal period of 10 days for meat is justified. The product is contraindicated for use in lactating sheep producing milk for human consumption.

Analytical Methods Used
The analytical method was by HPLC and was fully validated.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals
The applicant has conducted a controlled target animal tolerance study using the product in sheep. All doses were administered orally on one occasion. Parameters were evaluated by clinical examination and measurement of various blood chemistry and haematology values. No adverse effects were seen following doses of twice the recommended dose.

The product literature accurately reflects the type and incidence of adverse effects which might be expected at higher doses.

Resistance
The bibliography provided shows that ivermectin resistance occurs in sheep nematodes within the EU.Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

The clinical efficacy has been reviewed by reference to the published literature and the applicant has provided a large bibliography to support the proposed dose and indications.

The effective dose of 200 microgram/kg is well established.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The applicant has provided an extensive bibliography which adequately describes the toxicology of the active substance. Pharmacokinetic parameters have been published and confirmed to be relevant to this product by means of a bioequivalence study using a version of the pioneer product. User safety has been adequately appraised and the relevant warnings are considered to be sufficient. An environmental risk assessment is not necessary for a bibliographical application according to Annex 1 of Directive 2001/82/EC; suitable warnings in relation to environmental contamination are proposed. Data from residue depletion studies using the finished product justify the proposed withdrawal period of 10 days for meat and offal. The product is contraindicated for use in lactating sheep producing milk for human consumption.

An extensive bibliography supports efficacy of ivermectin at the recommended dose, against the parasites of sheep mentioned in the SPC. This is supported by the pharmacokinetic study which confirms that the product is bioequivalent to the product which was used in many of the published studies. The bibliography can therefore be accepted as relevant to Macromectin Drench. A target animal tolerance study using the finished product confirms it is well tolerated at twice the recommended dose.

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 Macromectin Drench for the treatment of sheep. The benefit risk assessment is positive.