IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Noromectin 10 mg/ml Solution for Injection for Cattle and Pigs

PRODUCT SUMMARY

EU Procedure number	IE/V/0104/001/MR
Name, strength and pharmaceutical form	Noromectin 10 mg/ml Solution for Injection for Cattle and Pigs.
Active substance	Ivermectin
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Generic application in accordance with Article 13 (i) (a) (iii) of Directive 2001/82/EC as amended.
Date of Authorisation	13th March 2000
Target species	Cattle and pigs
Indication for use	Treatment of infections by internal and external parasites (as listed in the SPC)
ATCvet code	QP54AA01
Concerned Member States	DE, EL, ES, FR, IT, NL, PT, IS

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

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.

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. Qualitative and Quantitative Particulars

The product contains the active substance ivermectin (10 mg/ml) and the excipients glycerol formal and polyethylene glycol 200.

The container/closure system consists of high density polyethylene vials with bromobutyl bungs and aluminium caps. The product is supplied in 50 ml, 100 ml, 250 ml, 500 ml and 1 L pack sizes.

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 active 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)

Pharmacological Studies
The product is a solution for injection for subcutaneous administration to cattle and pigs, containing 10 mg/ml ivermectin.
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 has carried out Good Laboratory Practice (GLP) compliant studies in cattle and pigs to compare the pharmacokinetics of ivermectin following administration of Noromectin 10 mg/ml Injection and the reference product Ivomec Injection (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.

User Safety
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
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

Residue Studies
The product is intended for use as a single administration in cattle and pigs. It contains 10 mg/ml ivermectin and is to be administered subcutaneously to cattle at a dose of 200 microgram ivermectin per kg, and to pigs at a dose of 300 microgram ivermectin per kg.

The applicant has conducted GLP compliant residue depletion studies using the final formulation in cattle and pigs.These show that concentrations of ivermectin in all tissues examined (liver, fat, kidney, muscle from injection site) depleted to below the MRL before the end of the withdrawal period.

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

	All mammalian food producing species	
Muscle	30 microgram/kg	For porcine species the fat MRL relates to ‘skin and fat’ in natural proportions.
Liver	100 microgram/kg	

Kidney	30 microgram/kg	
Fat/ skin	100 microgram/kg	
Milk	-	

Withdrawal Periods
Based on the data provided and calculations based on the adopted acceptable daily intake of ivermectin, a meat withdrawal period of 49 days for cattle and 18 days for pigs is justified.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

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant conducted GLP compliant, controlled target animal tolerance studies using multiples of the recommended dose in cattle and pigs. All doses were administered subcutaneously. In cattle a single dose was administered, and in pigs injections were repeated on consecutive days. Parameters evaluated included haematology and biochemistry as well as physical examination and post mortem examination of the injection sites.

No significant systemic adverse effects were seen following the administration of doses up to twice the recommended dose in cattle, or up to 3 times (repeated) in pigs, although local reactions occurred at the injection site in some animals. A second study was also carried out in cattle to evaluate injection site reactions following administration of Noromectin Injection. Non painful swellings commonly occurred.A clear mention of these effects appears on the label.

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.
In pigs, the applicant confirmed the equivalent efficacy by means of two studies using dose limiting nematode species.

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.

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:

Safety/Efficacy Changes

Summary of change **(Application number)**	**Approval date**
Reduction in the withdrawal period in swine from 35 days to 18 days (IE/V/104/001/II/005)	13/10/2008
Decision in respect of the Article 35 referral relating to marketing authorisations for veterinary medicinal products which contain the active substance ivermectin. (CRN 7007174)	14/01/2010