IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Noromectin 18.7 mg/g Oral Paste for Horses

PRODUCT SUMMARY

EU Procedure number	IE/V/0124/001/MR
Name, strength and pharmaceutical form	Noromectin 18.7 mg/g Oral Paste For Horses
Active substance(s)	Ivermectin
Applicant	Norbrook Laboratories (Ireland) Limited, Rossmore Industrial Estate, Monaghan, Ireland
Legal basis of application	Generic application in accordance with Article 13.1.a)(iii) of Directive 2001/82/EC as amended.
Date of Authorisation of procedure	6th April 2001
Target species	Horses
Indication for use	For the treatment of gastrointestinal parasites (as listed in the SPC)
ATCvet code	QP54AA01
Concerned Member States	AT, BE, DE, DK, ES, FI, FR, IT, LU, NL, PT, SE, UK, LU, 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 ivermectin and the excipients hydroxypropyl cellulose, hydrogenated castor oil, titanium dioxide (E171), water for injections and propylene glycol.
The container/closure system is low-density polyethylene pre-filled syringes containing 7.49 g of product in cartons of 1, 2 or 10 syringes.

The formulation of the batches used in key clinical studies are identical to that proposed for marketing.
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.

The product is manufactured using conventional manufacturing techniques.Process validation will be carried out on the first three production batches post authorisation.

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 have been provided.
Other substances in the product comply with the European Pharmacopoeia.

The product is packaged in low-density polyethylene pre-filled syringes. 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

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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

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 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

The manufacture of the product is adequately described and controlled.Testing methods and specifications for the raw materials and packaging components are acceptable. The control tests and specifications for the finished product are appropriate. The shelf life and storage conditions are supported by appropriate stability data.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

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.
The applicant conducted a Good Laboratory Practice (GLP) compliant study to compare the pharmacokinetics of ivermectin following administration of Noromectin Paste and the product Eqvalan Paste (Merial). The confidence intervals for the pivotal pharmacokinetic parameters (Cmax and AUC) were marginally above the allowable upper range for bioequivalence as defined in the current Bioequivalence Guideline. This was adequately explained by the expected variation in some individual horses.
The applicant conducted further safety studies with Noromectin Paste to show that this finding has no adverse effect on target animal or consumer safety; this conclusion was supported by an extensive bibliography which confirms the wide safety margin of ivermectin.

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 of200µg/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 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
The product is intended for use in horses. It contains 1.87% ivermectin and is to be administered orally as a single dose.

Residue Studies

A residue depletion study using the final formulation has been conducted in horses. 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 Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:The marker substance is 22,23 dihydroavermectin H2B1a.

	ALL MAMMALIAN SPECIES
Muscle	30 µg/kg
Liver	100 µg/kg
Kidney	30 µg/kg
Fat/ skin	100 µg/kg
Milk	-

Withdrawal Periods

Based on the data provided above, a withdrawal period of 34 days for meat is justified.
The product is not for use in mares producing milk for human consumption.
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 multiple doses of the product in horses. All doses were administered orally on two consecutive days. Parameters were evaluated by clinical examination and measurement of various blood chemistry and haematology values. No adverse effects were seen following repeated doses of five times the recommended dose.
The product literature accurately reflects the type and incidence of adverse effects which might be expected at higher doses.

Resistance
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 µg/kg is well established.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

This is a generic application based on the reference product Eqvalan Paste (Merial), which has the same qualitative and quantitative composition in terms of active substances, and has the same pharmaceutical form. In a GLP compliant pharmacokinetic study, the products were shown have very similar pharmacokinetics although Noromectin Paste was marginal more bioavailable. Further studies and bibliographical data confirm that there are no safety concerns associated with this.User safety has been adequately appraised and the relevant warnings are considered to be sufficient. An environmental risk assessment is not necessary for a generic 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 withdrawal period of 34 days for meat and offal. In conclusion, a similar profile to the reference product with respect to safety to humans and environmental safety can be assumed.
An extensive bibliography supports efficacy of ivermectin at the recommended dose, against the parasites of horses mentioned in the SPC. This is supported by the pharmacokinetic study which confirms that the product is comparable to the product which was used in many of the published studies. The bibliography can therefore be accepted as relevant to Noromectin Paste.
A target animal tolerance study using the finished product confirms it is well tolerated at five times 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 Noromectin Oral Paste for the treatment of horses. The benefit/risk 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:
Quality Changes

Summary of change	Approval date

(Application number)	
Change in the fill-weight/fill volume of non-parenteral mulit-dose products. IE/V/0124/001/1B/003	31st July 2006