ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Equimax Oral Gel for Horses

PuAR correct as of 24/07/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1 A

PRODUCT SUMMARY

EU Procedure number	UK/V/0156/001
Name, strength and pharmaceutical form	Equimax Oral Gel for Horses
Applicant	Virbac S.A. 1ére Avenue — 2065m — L.I.D. 06516 Carros Cedex France
Active substance(s)	Ivermectin & Praziquantel
ATC Vetcode	QP 54AA51
Target species	Horses
Indication for use	For the treatment of mixed cestode and nematode or arthropod infestations, due to adult and immature roundworms, lungworms, bots and tapeworms in horses: • Nematodes Large-strongyle: *Strongylus vulgaris* (adult and arterial larvae) *Strongylus edentatus* (adult and L4 tissue larval stages) *Strongylus equinus* (adult) *Triodontophorus spp.* (adult) Small-strongyle: Cyathostomum: *Cylicocyclus spp., Cylicostephanus spp., Cylicodontophorus spp., Gyalocephalus spp.* (adult and non-inhibited mucosal larvae). Parascaris: *Parascaris equorum* (adult and larvae). Oxyuris: *Oxyuris equi* (larvae).

	Trichostrongylus: *Trichostrongylus axei* (adult). Strongyloides: *Strongyloides westeri* (adult). Habronema: *Habronema spp.* (adult), Onchocerca: *Onchocerca spp. microfilariae* i.e. cutaneous onchocerciasis Lungworm: *Dictyocaulus arnfieldi* (adult and larvae). • Cestodes (Tapeworm): *Anoplocephala perfoliata, Anoplocephala magna, Paranoplocephala mamillana.* • Dipteran insects: *Gasterophilus spp.* (larvae) As tapeworm infestation is unlikely to occur in horses before two months of age, treatment of foals below this age is not considered necessary.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 5.10b of Directive 81/851/EEC.
Date of completion of the original mutual recognition procedure	17 January 2002
Date product first authorised in the Reference Member State (MRP only)	6 July 2001
Concerned Member States for original procedure	Repeat use procedure 2004 adding: Czech Republic, Germany, Hungary, Poland, , Slovakia, Slovenia Repeat use procedure 2003 adding: France Concerned Member States cited in Marketing Authorisations prior to 2003:- Austria, Belgium, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This application was originally made under the National procedure, it then underwent the Decentralised procedure, followed by three Repeat Use procedures. The legal basis for the application was defined by Directive 81/851/EEC as amended, Article 5. 10 (b), for products with known constituents previously unused in combination. Ivermectin had been previously authorised for use in horses in the product Eqvalan Paste for Horses. Equimax Oral Gel for Horses is administered as a single dose at 200 µg of ivermectin and 1.5 mg of praziquantel per kg bodyweight.

The product is an anthelmintic oral gel that has been shown as bioequivalent to Eqvalan Oral Paste for Horses, (for the ivermectin component), marketed by Merial Animal Health Ltd in the UK for over 15 years. 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[1].

[1] SPC – Summary of Product Characteristics.

The efficacy of the product was demonstrated according to the claims made in the SPC and the overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains Ivermectin (18.7 mg) and Praziquantel (140.3 mg) and excipients hydrogenated castor oil, hydroxypropylcellulose, titanium dioxide (E171) and propylene glycol.

The container/closure system consists of an adjustable multidose syringe constructed from high density polyethylene (white) and low density polyethylene (white). The syringe contains 6.42 or 7.49 grams of product and is fitted with variable dose capacity. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation of the product is justified and efficacy tests are provided below.

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. The method consists of several stages of mixing, with a heating and cooling stage half way through and colloidal milling once the mixture is satisfactory. The packaging is then filled and labelled.

C. Control of Starting Materials

The active substances are ivermectin and praziquantel, established active substances manufactured in accordance with the principles of Good Manufacturing Practice. The active substance specification is considered adequate to control the quality of the material, and both active substances have European Pharmacopeia (Ph. Eur) monographs. Ivermectin is tested by the dosage from manufacturer in order to check compliance with the Ph. Eur monograph. Praziquantel is also tested in compliance with data supplied in the Ph. Eur and in the United States Pharmacopeia. The applicant confirmed that praziquantel is presented as the racemate. The excipients are hydrogenated castor oil, hydroxypropylcellulose, propylene glycol and titanium dioxide (E171). All comply with monographs in the Ph. Eur.

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

A declaration of compliance with the combined CVMP/CPMP note for guidance EMEA/410/01 and the CVMP position paper EMEA/CVMP/019/01 on TSE risk was provided.

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. These tests include HPLC identifying the active substances, a purity test for degradation products and visual tests for the coloured excipient, titanium dioxide. Satisfactory validation data for these analytical methods have been provided and batch analytical data from 4 batches have been provided demonstrating compliance with the specification.

G. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product. Stability data on the finished 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.

Stability data were provided which showed that the active substances and finished product were stable for acceptable time periods. The finished product must not be stored above 30^{o}C. Opened syringes must be stored below 25^{o}C.

H. Genetically Modified Organisms

Not Applicable

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 6 months.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant provided bibliographical data which show that ivermectin acts by inhibiting nerve impulses. Its mode of action includes the glutamate-gated chloride ion channels. Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with subsequent hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the relevant parasites. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels.

Praziquantel acts by impairing both motility and function of the suckers of cestodes and trematodes. Its mode of action includes the impairing of neuromuscular co-ordination but also influences the permeability of the integument of the worms, which leads to excessive calcium and glucose loss. This induces spastic paralysis of the parasite musculature and subsequent death.

Pharmacokinetics

Extensive bibliographic data was provided. Ivermectin reaches peak plasma concentration in the horse within 24 hours, and studies have found that the concentration was greater than 2 ng/ml 14 days post-administration. The elimination half-life of ivermectin has been established as 90 hours. Peak plasma levels for praziquantel are reached within 1 hour. The active substance is rapidly eliminated and undetectable 8 hours post-treatment. The half-life has been established as being 40 minutes.

Toxicological Studies

Single Dose Toxicity

Ivermectin

The applicant provided bibliographical date from a variety of sources. Studies were conducted in mice, rats, rabbits, dogs, horses and Rhesus monkeys. Predominant symptoms of central nervous system disorders were observed within one hour of dosing, mostly consisting of tremors, depression, ataxia,

paresis, paralysis and death. LD_{50}[2] from a series of references (mg/kg) for the oral route for mice ranged from 25 – 80 mg/kg, with greater than 160 mg/kg seen for oral lavage, and one result for mice showing 30 mg/kg for the intraperitoneal route. For rats, the LD_{50} for oral gavage was from one reference was 42.8 mg/kg for males and 52.8 mg/kg for females, with 50 mg/kg observed for oral administration. Intraperitoneal LD_{50} was 55 mg/kg, dermal >660 mg/kg and inhalation LD_{50} >5.11 mg/litre. In rabbits, the LD_{50} was found to be 406 mg/kg for the dermal route. For Rhesus monkey, the LD_{50} via the oral route was found to be >24 mg/kg. For these series of studies, the LD_{50} in horses was not determined. When dosed intramuscularly with 12000 µg/kg (60 times the recommended dose), horses exhibited depression, mydriasis, ataxia, depressed respiratory rate, a drooping lower lip and transient decrease in serum iron levels. Death occurred in one animal. Mydriasis and absence of papillary response to light were observed where horses were administered 3000 or 6000 µg/kg ivermectin.

Praziquantel

From a series of referenced data from mice, rats, rabbits, dog and cats, the LD_{50} for mice was found to be 2454 mg/kg for the oral route, 7172 mg/kg for the subcutaneous route and >2000 mg/kg for the intramuscular route. For rats, the LD_{50} was found to be 2840 mg/kg for the oral route, >16000 for the subcutaneous route, >1000 for the intramuscular route and 796 for the intraperitoneal route. Rabbits exhibited an LD_{50} of approximately 1050 mg/kg via the oral route, with dogs exhibiting an of >200 mg/kg via the subcutaneous or oral routes, and cats >50 mg/kg via the oral, subcutaneous or intramuscular routes

Repeated Dose Toxicity

Sufficient published data were submitted for this section. Ivermectin was noted as having the greater toxicity of the two active substances.

Tolerance in the Target Species of Animal

Adverse effects consisting of ataxia, diarrhoea, central nervous system depression and generalised paresis of all four limbs were seen following 10 times the recommended dose of ivermectin in a 16 hour old foal. Bibliographical data has also been provided which show/s that the incidence of adverse reactions in horses has been 0.0003% based on tens of millions of doses. No adverse events were recorded in 8 horses given praziquantel at a dose of 0.75mg/kg orally, or in 11 horses given 1.0mg/kg orally.

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

[2] LD_{50} – half lethal dose.

Foetotoxicity (includingTeratogenicity), Mutagenicity, Carcinogenicity

Suitable data were received for all of these sections. Neither active substance was considered to be carcinogenic. Some evidence was seen of foetotoxicity at high levels of the active substances, when given to laboratory species. The dose regimen provided in the SPC should be adhered to.

Other Studies

Bibliographical data showing that mild to moderate toxic effects occur to specific organs when the active substances were applied individually to laboratory animals were submitted. Using the Equimax formulation, moderate but reversible effects were seen in a GLP[3] rabbit eye irritation test, and the formulation was not an irritant to rabbit skin, again, in a GLP-compliant test. Additionally no serious reactions were observed in a GLP-compliant guinea-pig skin sensitisation test.

Microbiological Studies

The applicant provided bibliographical data to show the actions of ivermectin against nematodes and arthropods. Praziquantel and ivermectin do not possess antifungal or antimicrobial activity, although some effects are seen when ivermectin is used at very high doses.

Observations in Humans

Both ivermectin and praziquantel have previously been used in human treatment. A suitable review of accidental or clinical administration of the active substances was provided.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which shows that the most likely potential exposure route to the user is accidental ingestion, for which acute oral toxicity tests are below the LD_{50}.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

This type of application is exempt from the requirement to submit ecotoxicity data as part of the application. This is in accordance with Point 5 (2) of Chapter 1 in Part 3 of Title I of the Annex of Directive 81/852/EEC. However, a Phase I environmental risk assessment was provided by the applicant.

It should also be noted that ivermectin has been used extensively in horses and comparisons have been made in the dossier with the pioneer product, Eqvalan Paste for Horses. Less data are available for the use of praziquantel products in horses.

[3] GLP – Good Laboratory Practice.

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that ivermectin is rapidly eliminated from the environment via photo-degradation or sequestration in soil, and praziquantel is inactivated by metabolism in the target species.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed:-

- Unused product and containers should be disposed of in accordance with national requirements.
- EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container.

III.B Residues documentation

Residue Studies

The applicant provided a study showing bioequivalence with the reference product Eqvalan, and also included a residue depletion study in the application as a parallel study to the above. This study showed in that horses the levels of the marker residue were below the MRL values in both liver and peri-renal fat at 28 and 35 days after administration. All relevant MRL data is the same as the reference product.

Pharmacologically active substance	**MRLs**	**Target tissues**
Ivermectin	15µg/kg 20µg/kg 15µg/kg 15µg/kg	Muscle Fat Liver Kidney

Praziquantel is entered into Annex II of Council Regulation (EEC) 2377/90.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 35 days for meat in Horses is justified.

IV CLINICAL ASSESSMENT (EFFICACY)

The legal basis for the application is that detailed in Directive 81/851/EEC as amended, Article 5, 10 (b). This is because the application deals with a new veterinary medicinal product containing known constituents not hitherto used in combination for therapeutic purposes. The requirements for such applications state that the results of pharmacological and toxicological tests and of clinical trials relating to the combination must be provided, but that it shall not be necessary to provide references relating to each individual constituent.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant conducted a controlled target animal tolerance study using 1, 3 and 5 times the recommended dose in the target species. A paste with the same formulation of active ingredients absent was used as a control. All doses were administered orally on a single occasion. Parameters evaluated were haematological parameters, blood biochemistry and clinical observation prior to administration, and 2 and 16 days post administration. No adverse effects were seen when the product was administered at 1, 3 and 5 times the recommended dose. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Pharmacology

The applicant provided bibliographical data to show that ivermectin increases membrane permeability to chloride ions in nematodes and arthropods. The precise mode of action of praziquantel has not been identified with certainty but there are many documented antiparasitic effects with various possible mechanisms described. Praziquantel induces a calcium ion influx across the integument, which is coupled to muscle cells. The result is a spastic contraction of the musculature, impairing motility and function of suckers in cestodes. There is also damage to the integument, exposing the parasite to immunological activity.

Data provided on pharmacodynamics and pharmacokinetics above is also relevant to this section, along with references cited.

Resistance

The bibliography provided suggests that serious resistance to ivermectin has developed in sheep and goats. However, there have been no reports of true ivermectin resistance in horse parasites. There also do not appear to be any reports of resistance specifically related to arthropods exposed to ivermectin.
As praziquantel is used for treatment of schistosomiasis in man there have been concerns of resistance. However, there is little published literature concerning resistance in animal parasites.

As the two active substances have widely differing modes of action, the combination is not expected to influence the development of resistance to ivermectin or praziquantel. Adequate warnings and precautions appear on the product literature

IV.B Clinical Studies

Laboratory Trials

The applicant conducted a dose confirmation study.

Dose confirmation studies:

Study title	Study testing the product on horses naturally infected with bots and nematodes.
Objectives	To test the efficacy of 0.2mg Ivermectin per kg body weight.
Test site(s)	Multi-centre study.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Equimax oral paste (Ivermectin, Praziquantel), 0.2mg/kg BW once.
Control product/placebo	Equimax oral paste containing praziquantel only.
Animals	62 horses, 31 in control group, 31 in treatment group. *All horses naturally infected with bots and nematodes.*
Outcomes/endpoints	Primary (NOT secondary endpoints) Significant reduction in worm count or faecal egg count.
Randomisation	Randomised.
Blinding	Single, blinded study.
Method	Study schedule. In each country, horses of each group were treated and observed in parallel as a study population, or as independent replicates. After a 7-day period of acclimatisation, horses were treated on Day 0 according to the treatment group. From Day 7 to Day 14, daily clinical examinations were performed, and faecal samples collected on Days 7 and 14. At Day 14, horses were slaughtered and a complete post-mortem examination for parasite collection and identification was performed.
RESULTS	
Outcomes for endpoints	Statistical data were collected which confirmed the efficacy of the test product.
DISCUSSION	The Ivermectin component in the product demonstrated satisfactory efficacy against a wide range of nematodes and bots and did not appear to be affected by combination with praziquantel. No adverse events were recorded during this study.

Field Trials

Study title	Study to compare efficacy of Equimax Oral Paste with Eqvalan.
Objectives	Assess the prevalence of double infection (tapeworms and nematodes) in horses, and to compare efficacy of Equimax oral paste with that of Eqvalan.
Test site(s)	Multi-centre, EU-based .
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Equimax (praziquantel 1.5mg/kg and ivermectin 0.2mg/kg), given as a single dose and observed for 21 days.
Control product/placebo	Reference product – Eqvalan
Animals	*940 horses analysed, in which 264 were free of nematodes and cestodes, 435 were infected with nematodes only, 92 were infected with cestodes only and 149 were infected with both cestodes and nematodes. 389 horses entered the efficacy study, of which the data for 357 were analysed (269 in the Equimax group and 88 in the Eqvalan group) participants ranged from 1-24 years of age and weighed from 150-720kg*
Outcomes/endpoints	Primary (NOT secondary endpoints) reduction in faecal egg count.
Randomisation	Randomised.
Blinding	None
Method	Study schedule. In the efficacy part of the trial, horses were treated at Day 0 and observed for a period of 21 days. Three faecal samplings were performed: (1) at Day 0 (before treatment), (2) at Day 14, and (3) at Day 21
Statistical method	
RESULTS	
Participant flow	All of the 88 individuals in the Eqvalan group completed the study protocol without event. 2 of the 269 individuals in the Equimax group suffered adverse events.
Outcomes for endpoints	Statistical data were collected which confirmed the efficacy of the test product.
Adverse events	2 adverse events were reported in the group tested with Equimax – colic and circulatory disturbance. These were not considered to be related to treatment.
DISCUSSION	There was high efficacy (more than 90% in all cases) for the product against nematodes and cestodes, in multiple geographical locations and environments. This study also not only provided evidence of efficacy of Equimax in comparison with Eqvalan Paste, but also provided useful information on the prevalence of helminth infestations in

	horses. As only 2 adverse events were reported, neither of them considered to be due to the product, there is good evidence to suggest the product is safe for use in the target species at recommended dose following instructions on the SPC and product literature.

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.

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)