IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Eraquell Tabs, 20 mg Chewable tablets for Horses

PRODUCT SUMMARY

EU Procedure Number	formerly (UK/V/0330/001)
Name, Strength, Pharmaceutical Form	Eraquell Tabs, 20 mg Chewable tablets for Horses
Active Substances(s)	Ivermectin
Applicant	Virbac 1ère avenue 2065 M LID 06516 Carros France
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target Species	Horses
Indication For Use	For the treatment of nematode and arthropod infestations due to adult and immature roundworms and bots in horses. **Nematodes** Large-strongyles: *Strongylus vulgaris* (adult and arterial larvae) *Strongylus edentatus* (adult and L4 tissue larval stages) *Strongylus equinus* (adult and L4 larval stage) *Triodontophorus* spp.(adult) Small-strongyles: Cyathostomum (adult and non-encysted mucosal larvae)*: Cylicocyclus* spp.*, Cylicostephanus* spp., *Gyalocephalus* spp. Parascaris: *Parascaris equorum* (adult and larvae). Oxyuris: *Oxyuris equi* (adult and larvae). Trichostrongylus: *Trichostrongylus axei* (adult). **Dipteran insects**: *Gasterophilus* spp.(larvae).
ATC Code	QP54AA01
Date of completion of the original decentralised procedure	29 April 2009 (UK) 01 October 2009 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SK, SI, 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

Eraquell Tabs, 20 mg Chewable Tablets for Horses contain 20 mg ivermectin per 3.3g tablet, and are intended for the treatment of a variety of nematode and arthropod infestations in horses. Infestations in horses may be due to adult and immature

roundworms and bots, and the product is directed against the following species: Large-strongyles; *Strongylus vulgaris* (adult and arterial larvae), *Strongylus edentatus* (adult and L4 tissue larval stages), *Strongylus equinus* (adult and L4 larval stages), and *Triodontophorus* spp., (adult). Small-strongyles; Cyathostomum (adult and non-encysted mucosal larvae): *Cylicocyclus* spp., *Cylicostephanus* spp., and *Gyalocephalus* spp. In addition, the product may be used against *Parascarisequorum*, (adult and larvae), *Oxyuris equi* (adult and larvae), *Trichostrongylusaxei* (adult), and Dipteran insect species, *Gasterophilus*. The dosage for the product is 1 tablet/100 kg bodyweight as a single, oral administration.
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 and the slight reactions observed are indicated in the SPC. The product is not to be used in foals under two weeks of age, and is not to be used in horses known to be sensitive to the active ingredient or the excipients.
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. Composition
The product contains 20 mg ivermectin per tablet and excipients povidone 30, crospovidone, cellulose, cider applemarc, glucose, starch, compressible sugar and magnesium stearate. All ingredients apart from compressible sugar and cider applemarc are monographed in the European Pharmacopoeia. Compressible sugar used in this product is of a quality accepted by the United States National Formulary, and cider applemarc, the formulation of which is controlled by established and accepted procedures, has been used previously in the product Equimax Tabs 150 mg/ 20 mg Chewable Tablet for Horses.
The container system is a white, opaque, cylindrical and rigid polypropylene tube, closed by a child-resistant, polyethylene cap.
The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the formulation and the absence of preservative are justified.
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, and the product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.
The manufacturing process was validated by analysis of three batches, from which the granules were tested for particle size distribution, flowability and apparent density. Homogeneity of tablets formed from the granules was analysed, including uniformity of mass, thickness and diameter and uniformity of content. Dissolution of ivermectin within the tablets was also analysed. All tests were satisfactory.

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 have been provided, with data being provided on three 100kg batches of ivermectin. Test results showed complete compliance with the relevant certificate of analysis.
A suitable Certificate of European Pharmacopoeia (CEP) was provided, confirming the suitability of the proposed source of ivermectin for the product.
Microbiological tests and production methods applied specifically to cider applemarc comply with those described in the European Pharmacopoeia.
All excipients apart from compressible sugar and cider applemarc were shown to be in accordance with monographs in the European Pharmacopoeia. Compressible sugar is monographed in the United States National Formulary.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
A signed declaration stating that the product complies with CPMP/CVMP guidelines on TSEs was provided. In addition, a declaration was provided which stated that magnesium stearate used in the manufacture of the product is of vegetable origin, and a UK Format 3 statement was also supplied. These documents were considered acceptable.

E. Control on Intermediate Products
Not applicable.

F. Control Tests on the Finished Product

A series of tests are applied prior to the release of the finished product. Tests include a visual inspection of the product as packaged for sale, tablet size and diameter, water content, friability, crushing resistance of the tablet, package seal integrity, HPLC/UV spectrum analysis of ivermectin, dissolution, microbiological analysis, and ivermectin impurities.

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests on 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 have been provided demonstrating compliance with the specification.

G. Stability

No stability data were provided for ivermectin. The certificate of suitability for the raw material states that a three year retest interval is appropriate when the material is stored in a double-lined polyethylene heat-sealed bag and placed in an aluminium tin.
Tablets were stored as 150kg pilot scale batches under VICH conditions at a variety of temperatures and humidity, for time periods of up to 36 months.
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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The shelf life of the product as packaged for sale is 36 months, and shelf-life after first opening of the immediate packaging is 12 months.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided bibliographical data describing the origin and action of ivermectin. Ivermectin is one of a series of large molecular weight substances formed in the mycelia of the mould, *Streptomyces avermitilis* and belongs to the avermectins, compounds structurally similar to complex 16-membered macrolcyclic lactones. The predominant effect of ivermectin is the increase in permeability of chloride ions within the parasite membrane. This results in the disruption of GABA-mediated transmission in the peripheral nerves, causing irreversible paralysis and death. A series of bibliographic data described the use of ivermectin and other avermectins in studies on cattle, sheep, goats, pigs, horses, cats and dogs, all of which demonstrated the efficacy of these compounds.

The applicant also provided bibliographical data which described the absorption, metabolism and excretion of ivermectin. One study in cattle, sheep and rats used titrium-labelled ivermectin. In cattle, the highest tissue residues were seen via intraruminal and subcutaneous routes in the fat and liver tissue, with half-lives of 6-8 days for the former and half-lives of 4-5 days for the latter. Shorter half lives were seen in rats and sheep. The tissue distribution of ivermectin was essentially similar for cattle, sheep and rats, and similar in male and female rats. Residues of ivermectin were seen to increase proportionately with dose, and when delivered via a variety of routes, the drug diminished at a similar rate, regardless of dosing route. Ivermectin was excreted primarily in the faeces in the three species studied.

Another study in sheep noted that low feed intake contributed to the efficacy of ivermectin, while other data concluded that ivermectin was more efficacious when used subcutaneously than orally in reindeer. A further study confirmed the same on results in tests in horses and sheep. Additional data was provided on the use of ivermectin in horses, the mean plasma residence time for which was found to be 4.8+/-0.6days.

Toxicological Studies

The applicant provided bibliographical data describing the use of ivermectin in relation to a series of toxological studies.

- Single Dose Toxicity

Bibliographic data were provided describing the established LD50 for a variety of species. In horses dosed intramuscularly with 12000 µg/kg ivermectin, (which equates to 60 times the recommended dose), symptoms noted were depression, mydriasis, ataxia, depressed respiration, drooping lower lip and a transient decrease in levels of iron in the blood serum. Mydriasis and absence of papillary response were observed in horses receiving 3000 µg/kg or 6000 µg/kg of ivermectin.

- Repeated Dose Toxicity

Bibliographic data summarised the no effect level (NOEL) of ivermectin in several species. In rat the NOEL was 0.4 mg/kg/day, and in monkey the NOEL was 1.2 mg/kg/day. A study on tolerance in the target species was cited, which used ivermectin and praziquantel as a paste (Equimax Oral Gel formula), at the therapeutic dose, and three and five times the therapeutic dose. The paste was well tolerated at five times the recommended dose. Additional data included the results of histological studies. The data presented for tolerance confirmed that ivermectin is well tolerated in horses at the recommended dose.

- Reproductive Toxicity

Bibliographic data were provided with regard to the effect of ivermectin on reproductive toxicity in rats and dogs. In rats, toxic effects were seen when the drug was given orally at 1 mg/kg bodyweight during gestation. Effects observed included decreased cliff avoidance and decreased pivoting and forward locomotion. At 4 mg/kg bodyweight, when ivermectin was given during gestation and lactation, all pups died. In another study in rats, an increased gestation period was seen in rats given 3.6 mg/kg bodyweight/day, and the weight of pups reduced.

In dogs, an effect was seen on male fertility when ivermectin was given at 0.6mg/kg.

- Tolerance in the target species

A GLP compliant study analysed the effects of the therapeutic dose, and three times and five times therapeutic doses of ivermectin and praziquantel in horses. An ivermectin/praziquantel oral paste was evaluated in young horses, and the paste was well tolerated at five times the therapeutic dose. Other studies were described all of which verified the tolerance of ivermectin for use in horses at five times the recommended dose. Refer to Part IV of this report for full details.

- Mutagenicity

No effects were reported in mutagenicity studies.

- Carcinogenicity

An account of rats dosed orally with up to 2mg/kg abamectin, (no published data for ivermectin), for 105 weeks and mice dosed with up to 8 mg/kg for 94 weeks was given. No carcinogenic effects were seen.

Other Studies
The applicant has provided bibliographical data providing information on several additional studies using ivermectin. In one study, rats were exposed to inhaled ivermectin at 5.11mg/l for 60 minutes. Mucosal irritation was seen. In another study, 100 mg of ivermectin in a powderised form produced only minimal eye irritation when applied to the eye of a rabbit. In an additional study, ivermectin was seen to increase lymphocyte count in the rabbit. A further study reported a comparison of moxidectin gel and ivermectin paste in infected horses in which no adverse reactions were seen.

Observations in Humans
The applicant provided information describing four instances of accidental or therapeutic use of ivermectin in humans. No adverse reactions were reported in these instances where the drug had entered the body at a dose of 200 µg/kg bodyweight, or at a dilution of 1%.

Microbiological Studies
The applicant has provided bibliographical data explaining that ivermectin has no antifungal or antiprotazoal activity, and has antimicrobial activity only at very high doses.

- Studies on Metabolites, Impurities, Other Substances and Formulation.

A number of studies were performed using the final formulation for Eraquell Tabs, 20 mg Chewable Tablets for Horses. These studies were an acute oral toxicity study and an acute dermal toxicity study in rats, an eye irritation study in rabbits a skin irritation study in rabbits and a skin sensitisation study in guinea pigs. Ivermectin was evaluated as producing low oral and dermal toxicity, and considered as being a weak eye irritant. No skin irritation or sensitisation was seen.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which identifies potential routes of exposure to the user.

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

- Wash hands after use.
- Avoid contact with the eyes. In the event of accidental contact with the eyes, rinse immediately with plenty of water. In case of eye irritation, seek medical attention.
- Do not eat, drink or smoke while handling this product.
- In the event of accidental ingestion, seek medical advice and show the package leaflet to the physician.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required.

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

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local 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 bibliographical data in support of the pharmacokinetics of ivermectin. Two reports were presented comparing Equimax, (a product similar to Eraquell Tabs containing ivermectin and Praziquantel), with Eqvalan Paste, a product containing ivermectin only. Bioequivalence was determined for two ivermectin-containing oral formulations in horses, and these data were considered to be relevant for Eraquell Tabs, 20 mg Chewable Tablets for Horses.

Residue depletion studies using the formula for Equimax Oral Gel (containing ivermectin and praziquantel) and Ivermectin Oral Paste at the maximum recommended dose were presented. For the first study on Equimax Oral Paste, two groups of horses were administered the recommended oral dose of Equimax at 28 or 35 days. Subsequent to slaughter, samples of liver and peri-renal fat were analysed, and level marker residue H_2B_{1a} values were seen to be below the maximum residue limit (MRL) in both tissues at both time points. In the second study on Ivermectin Oral Paste, even though the formulation was different, residues were well below the MRL in all 4 animals tested after 30 days.

Statistical analysis of the results was used to set the withdrawal period for Eraquell Tabs, 20 mg Chewable Tablets for Horses.

The analytical method used to detect ivermectin in fat and liver involved an isocratic reverse HPLC analysis of fluorescently-converted ivermectin and other derivatives. The method was fully validated.

Eraquell Tabs, 20 mg Chewable Tablets for Horses and Equimax were found to be bioequivalent with Eqvalan Paste with regard to ivermectin content.

MRLs

A table of MRLs was provided.

All mammalian food-producing species	MRLs (µg/kg)
Liver	100
Kidney	30
Fat	100

Withdrawal Periods

Based on data provided, a withdrawal period of 35 days for meat and offal was justified. Not permitted for use in horses producing milk for human consumption.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data giving comprehensive details of the mode of action of ivermectin in cattle, dogs, pigs, sheep goats and horses.

· Pharmacodynamics

Ivermectin acts by inhibiting nerve impulses, binding selectively to sites closely associated with the binding site of GABA and with chloride ions. Ivermectin increases membrane permeability to chloride ions leading to a change in membrane permeability, which results ultimately in the irreversible blocking of neurotransmission, and subsequent paralysis and death of the target parasite. References from published literature were cited giving dose-determination data for the use of ivermectin in horses.

Data were also provided on the effects of ivermectin in man, neonatal animals (rats), and collie dogs. Adverse effects seen in these species seem to be linked to the increased permeability of the blood-brain barrier. GABA is only present in the central nervous system in mammals, and ivermectin may cause adverse effects if the permeability of the blood-brain barrier is increased. This may occur in very young animals and in certain species of dog.

The applicant provided reports of dose-determination studies showing that ivermectin, when used as an oral paste in horses, is 90% effective at a dose rate of 200 µg/kg against target parasites. The reports reflected the proposed final dose for Eraquell Tabs, 20 mg Chewable Tablets for Horses.

· Pharmacokinetics

The applicant has provided bibliographical data giving comprehensive details of the metabolism of ivermectin in cattle, sheep, rats, pigs, reindeer and horses.

It was noted that although plasma concentrations of ivermectin persist longer after subcutaneous administration, this is not a route well tolerated in horses and therefore the oral route is more appropriate. Ivermectin used in oral paste at 200 µg/kg has been seen to be extensively distributed in horse plasma. In one study, a dose of ivermectin given at 200 µg/kg was detectable in plasma between 30 minutes and 30 days post-treatment. C_{max} was 44 ng/ml, T_{max} was 0.384 and mean resistance time was 4.78 days. Ivermectin is poorly metabolised and is cleared slowly from the body system, with metabolites being formed in the liver and in fat. The primary route of excretion of ivermectin is via the faeces.

Four studies on Equimax Tabs were provided by the applicant and were considered as having relevance with regard to bioavailability for the final formulation of Eraquell Tabs. One new report was submitted for the final formulation for Eraquell Tabs, and these were shown to be effective.

Tolerance in the Target Species of Animals

The applicant provided data which showed that Equimax Oral Gel, a product similar to Eraquell Tabs was the cause of four adverse reactions. There was one accidental ingestion in a dog, the other three were allergic reactions to, or gastro-intestinal reactions to major parasite lysis. The SPC carries suitable warning to abrogate adverse reactions.

Three reports in horses using Equimax Oral Gel and one on Equimax Tabs were provided. Both products contain ivermectin and praziquantel.

In the first study, twenty-four young horses were divided into four groups. The first group received a placebo paste at five times the dose rate and the remaining groups received single, three times and five times the recommended dose rate of the ivermectin/praziquantel paste, (Equimax Oral Gel). The dose of ivermectin received was 0.2, 0.6 or 1.0 mg/kg bodyweight, given as a single treatment. Biological and biochemical examinations were performed at various time points, and at necropsy, all animals were analysed macroscopically, with histological samples being taken for the tongue, liver kidney and spleen. For all dosage regimes, no adverse effects were seen.

The second study to observe the effects of ivermectin on reproduction in horses, ten in-foal mares received a placebo, and eleven in-foal mares received Equimax Oral Gel at three times the recommended dose, given as a single treatment. Neither mares, nor foals born during the study suffered adverse effects from the use of ivermectin.

A third study was designed to observe the effects of ivermectin on breeding stallions. Twenty-four stallions were divided into two study groups. The first group received Equimax Oral Gel at three times the recommended dose for three treatments. A variety of parameters relating to the reproductive capability of the stallions was observed, no clinically significant adverse results were seen.

Equimax Tabs were used in a fourth study in which twenty-four horses were divided into four treatment groups receiving no treatment, one times the recommended dose, three times the recommended dose or five times the recommended dose, (200µg/kg ivermectin, 150 mg/kg praziquantel). No clinically significant adverse effects were seen.

Finally, the applicant submitted details of a study using the final formulation proposed for Eraquell Tabs, 20 mg Chewable Tablets for Horses. This was a randomised, controlled, target species, single-dose safety study on twenty-four horses. Animals were placed into four treatment groups and administered one, three or five times the recommended 200 µg/kg dose, or received no treatment. Observations and biochemical examinations were made at different time points, and the animals necropsied at the end of the study. No adverse effects were seen.
Data from all relevant studies confirmed that Eraquell Tabs, 20 mg Chewable Tablets for Horses were safe and effective for use in the target species.

Resistance
A series of references were provided by the applicant, describing the effectiveness of ivermectin when used in horses to control parasites, and also instances of resistance to the compound. In the USA and Europe, studies indicated susceptibility of horse strongyles to ivermectin, even when there was resistance to other classes of anthelmintic. Other evidence in studies performed in the USA suggested that intensive use of ivermectin may lead to resistance. There have been isolated instances of resistance to ivermectin, indicating that global strategies are required to control it its use. There would appear to be some resistance to ivermectin emerging in *Parascaris equorum*, particularly in foals where high treatment frequency may occur.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies
Laboratory Trials
The applicant conducted several dose determination and confirmation studies. Two studies designed for the previously authorised Equimax Tabs (using Equimax Oral Gel and Equimax Tabs) were relevant to the new product, Eraquell Tabs, 20 mg Chewable Tablets for Horses. In addition, two new dose-confirmation studies were provided using the formulation for Eraquell Tabs. In the first two studies using Equimax Oral Gel and Equimax Tabs, no adverse effects were seen, and the concentration of ivermectin in the products was effective in combating bots, nematodes and roundworms.
In the first dose-confirmation study using the formula for the newly proposed product, seventy-two horses of different ages and from three countries were randomised into three treatment groups in two replicate sets of twelve horses each. Each naturally-infected animal received a single dose of either the test product (20 mg ivermectin per tablet), a placebo tablet, or the reference product, Equimax Oral Gel. Horses were clinically examined periodically, and subsequent to necropsy, examined for parasite infestation.
The tablets used in the study gave a comparable result to the reference product, no adverse effects occurred during treatment, and the product was effective against target parasites.
In the second study using the formula for the newly proposed product, Eraquell, effectiveness against three additional parasite species was examined in parasite-challenged horses. Eighteen horses were challenged with the parasites *S. vulgaris, S. equinus* and *S. edentatus*. Each horse received a single dose of the proposed product formula, a placebo, or a positive control product, Equimax Oral Gel. At necropsy, the animals were examined for parasites. There were no adverse reactions during treatment and the effectiveness of the proposed product matched that of the positive control.

Field Trials
A field trial had been previously conducted using the Equimax Oral Gel formulation, for the authorisation of Equimax Tabs. These data were considered appropriate for the evaluation of Eraquell Tabs, 20mg Chewable Tablets for Horses. The study was a muticentric, controlled and randomised field trial carried out in six countries and conducted in two parts. The first part of the trial assessed the prevalence of infection with both nematodes and tapeworms in horses, and the second part of the trial compared the efficacy of Equimax Oral Gel with Eqvalan, (an ivermectin-only containing paste) in combating natural infections of tapeworms and nematodes.
940 horses were observed for the prevalence study. The horses had either a cestode or a nematode infection, or both. This study provided data on the number and prevalence of cestode and nematode infections.
For the efficacy study, 389 horses were treated at day 0 and faecal samples taken at days 0 (before treatment), 14 and 21 for egg count. Some horses were given the Equimax Oral Gel formula, and some Eqvalan. 269 animals in the Equimax Oral Gel formula group and 88 in the Eqvalan group were assessed for parasite infection. Both products were effective against nematodes, there was however, a lack of efficacy against cestodes with ivermectin. No lessening of the effectiveness of ivermectin, (where effectiveness was observed), was seen when given in combination with praziquantel.
A palatability study was also performed on the Equimax Tabs final formula, and together with efficacy information provided for Equimax Oral Gel, these data were considered acceptable for the authorisation of Eraquell Tabs, 20 mg Chewable Tablets for Horses.

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

None.