ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Alverin 18.7 mg/g Oral Paste for Horses

Date created: 25th September 2014

PuAR correct as of 09/11/2018 when RMS was transferred to FR.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0512/001/DC
Name, strength and pharmaceutical form	Alverin 18.7 mg/g Oral Paste for Horses
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substance(s)	Ivermectin
ATC Vetcode	QP54AA01
Target species	Horses
Indication for use	The product is indicated for the treatment parasitic infestations in horses due to: **Large strongyles** *Strongylus vulgaris* (adults and arterial larval stages) *S. edentatus* (adults and tissue larval stages) *S. equinus* (adults) *Triodontophorus spp.* (adults) *Triodontophorus brevicauda* *Triodontophorus serratus* *Craterostomum acuticaudatum* (adults) **Small Strongyles** Adults and immature (fourth stage larvae) small strongyles or cyathostomes including benzimidazole-resistant strains: *Coronocyclus* spp. *Coronocyclus coronatus* *Coronocyclus labiatus* *Coronocyclus labratus* *Cyathostomum* spp. *Cyathostomum catinatum* *Cyathostomum pateratum* *Cylicocyclus* spp. *Cylicocyclus ashworthi* *Cylicocyclus elongatus*

	Cylicocyclus insigne *Cylicocyclus leptostomum* *Cylicocyclus nassatus* *Cylicocyclus radiatus* *Cylicostephanus* spp. *Cylicostephanus asymetricus* *Cylicostephanus bidentatus* *Cylicostephanus calicatus* *Cylicostephanus goldi* *Cylicostephanus longibursatus* *Cylicostephanus minutus* *Cylicodontophorus* spp. *Cylicodontophorus bicornatus* *Gyalocephalus capitatus* *Parapoteriostomum* spp. *Parapoteriostomum euproctus* *Parapoteriostomum mettami* *Petrovinema* spp. *Petrovinema poculatum* *Poteriostomum* spp. *Poteriosstomum imparidentatum* **Lungworms** (adult and immatures) *Dictyocaulus arnfieldi* **Pinworms** (adult and immatures) *Oxyuris equi* **Ascarids** (adults and third & fourth stage larvae) *Parascaris equorum (see section 4.4)* ***Hairworms*** *(adults)* Trichostrongylus axei **Large-mouth stomach worms** (adults) *Habronema muscae* **Neck threadworms** (microfilariae) *Onchocerca spp.* **Intestinal threadworms** (adults) *Strongyloides westeri* **Stomach bots** (oral and gastric stages) Oral and gastric stages of *Gasterophilus* spp.

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	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	18th June 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Finland, France, Germany, Hungary, Italy, Luxembourg, The Netherlands, Norway, Poland, Spain

I. SCIENTIFIC OVERVIEW

Alverin 18.7 mg/g Oral Paste for Horses has been developed as a generic of Eqvalan Oral Paste for Horses, which has been authorised in the UK since April 1994. Bioequivalence with the reference product has been determined. The product contains 18.7 mg/g ivermectin and is indicated for the treatment of parasitic infections in horses. The product is contraindicated in species other than the target species as severe adverse reactions can occur, including fatalities in dogs.

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[1].

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.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains 18.7 mg/g ivermectin and the excipients maize oil, polysorbate 80, apple flavour and silica colloidal anhydrous.

The container/closure system consists of dose graduated disposable polyethylene oral syringes containing 6.42 g of product and packaged in cartons containing 1 or 20 syringes. 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. The product is manufactured by mixing the maize oil and polysorbate 80 with the apple flavour. The ivermectin is added and mixed before slowly adding the silica colloidal anhydrous to make a homogenous paste which is filled into syringes. Process validation data on the product have 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 (Ph. Eur). Ph. Eur. Certificates of Suitability have been provided for both manufacturers of the active substance. 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.

The excipients are manufactured in accordance with the relevant Ph. Eur. monographs. The apple flavour is not described in a pharmacopeia and an in-house specification has been provided.

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

Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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. The tests include those for identification and assay of the active substance, viscosity, syringeability, total viable aerobic count and *E. coli*.

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

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. The active substance is supplied in accordance with Ph. Eur. Certificates of Suitability and the retest period is 3 years for one manufacturer and 2 years for the other manufacturer of the active substance.

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. Data were provided for batches stored at 25°C/60% RH for 36 months and 40°C/75% RH for 6 months. The data support a shelf life of 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale is 2 years.
- This is a single use product. The cap should be replaced after use and remaining product should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main route of exposure is accidental dermal and ocular contact during administration. The risk to the user is low due to the small quantities handled at a time and as the ingredients are not skin sensitisers. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- Do not smoke, eat or drink while handling the product.
- Wash hands after use.
- This product may cause skin and eye irritation. Therefore, the user should avoid contact of the product with the skin and the eyes. In the case of contact, rinse immediately with plenty of water.
- In the case of accidental ingestion or eye irritation after contact seek medical advice immediately and show the package leaflet or the label to the physician.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment (ERA) in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is for individual use in a minor species. Although the animals are reared on pasture and ivermectin will enter the environment through direct excretion of faeces onto pasture, Phase II ERA's have previously been performed for ivermectin in cattle, a major species. The $PEC_{soil\ initial}$[2] has been calculated as 0.48 µg/kg for horses and 0.33 µg/kg for ponies. The results demonstrate that the environmental exposure will not be greater following use in the minor species. A Phase II assessment was not required. The Phase II assessments previously performed for the major species indicate high toxicity of ivermectin to dung fauna and aquatic organisms.

[2] PEC – Predicted Environmental Concentration

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

- Long term effects on dung insects caused by continuous or repeated use cannot be excluded. Therefore repeat treatments on a pasture within a season should only be given on the advice of a veterinarian.
- EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE.
  Do not contaminate ponds, waterways or ditches with the product or used container.

III.B Residues documentation

Residue Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of residue depletion studies are not required.

MRLs

MRLs for ivermectin are listed below:

	All mammalian food producing species
Liver	100µg/kg
Kidney	30µg/kg
Fat / skin	100µg/kg
Milk	Contraindicated

MRLs are not required for polysorbate 80 and silica colloidal anhydrous, whilst maize oil is considered out of scope. The apple flavour used in the product has been shown not to have pharmacological activity and can be permitted for use in the product with no further residue data required.

Withdrawal Periods

The same withdrawal period as the reference product was accepted.

- Meat and offal: 21 days
- Do not use in mares producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, pharmacodynamic data are not required.

Pharmacokinetics

Two bioequivalence studies were submitted to compare the test product and the reference product.

In the first study the test product and reference product were administered orally at the recommended dose rate, 200 µg ivermectin per kg bodyweight, to 20 healthy geldings. The horses were divided into two groups; Group A received the test product on Day 0 whilst Group B received the reference product. There was a 28 day wash-out period and on Day 48 horses were given the other treatment, so Group A received the reference product and Group B the test product.

Following administration blood samples were taken at regular intervals for up to 672 hours. All animals received a clinical examination within 12 hours and 48 hours after administration, as well as observation for local and systemic reactions throughout the trial. The ivermectin concentration was measured from the blood samples and the AUC[3], C_{max}[4] and T_{max}[5] were calculated. Statistical analysis on the pharmacokinetic parameters was performed by determining the 90% confidence intervals (CI) to compare bioequivalence, and ANOVA was used to compare treatment effect.

The results showed a similar pharmacokinetic profile for both products. The mean AUC for the reference product was 2765 compared to 2817 for the test product. The mean C_{max} was 39.27 µg/l and 40.44 µg/l for the reference and test products respectively. The mean T_{max} for the reference product was 9.45 hours and for the test product was 8.35 hours. The 90% CI were calculated for each of the parameters and for bioequivalence to be accepted should fall within a predefined limit (0.80 – 1.25). The upper and lower confidence intervals for AUC (0.89 – 1.18) and C_{max} (0.84 – 1.21) fell within the range, whilst for T_{max} (0.62 – 1.24) the lower limit was outside the range.

ANOVA analysis compared the difference between the three parameters and found no statistically significant difference ($P > 0.05$). No systemic clinical reactions were observed and all localised conditions were considered unlikely to be related to treatment.

It was concluded that whilst bioequivalence was demonstrated for the AUC and C_{max} it was not proven for the T_{max}. The statistical analysis using ANOVA indicated that no significant difference was present between the pharmacokinetic parameters. However bioequivalence could not be accepted for the test product with the reference product based on this study alone.

A second bioequivalence study was submitted. The study aimed to determine the bioequivalence of the test product with the reference product. The study involved 12 healthy horses, both male and female, which were given both products at a dose rate of 200 µg/kg orally. The horses were divided into two treatment groups; Group A received the reference product on Day 0 whilst Group B received the test product then on Day 48 Group A were given the test

[3] AUC – Area Under the Curve (Concentration curve)
[4] C_{max} – Maximum plasma concentration
[5] T_{max} – Time to maximum concentration

product and Group B the reference product. All animals had been fasted prior to treatment.

Following administration blood samples were taken at regular intervals for up to 504 hours. All animals were observed for local and systemic reactions at least twice daily throughout the trial. The ivermectin concentration was measured from the blood samples and the pivotal parameters AUC and C_{max} were calculated and transformed, in addition the T_{max} was determined alongside other ancillary parameters. Statistical analysis on the pharmacokinetic parameters was performed by determining the 90% confidence intervals (CI) to compare bioequivalence and ANOVA was used to compare treatment effect.

The results showed a similar pharmacokinetic profile for both products. The mean Ln(AUC) for the reference product was 8.1824 compared to 8.2716 for the test product. The mean Ln(C_{max}) was 4.1508 and 4.2671 for the reference and test products respectively. The mean T_{max} for the reference product was 4.7083 hours and for the test product was 4.3750 hours. The 90% CI were calculated for each of the parameters and for bioequivalence to be accepted should fall within a predefined limit (80 – 125%). The upper and lower confidence intervals for AUC (100 – 120%), C_{max} (101 - 125%) and T_{max} (84 – 102%) fell within the range. In addition the P value was calculated to determine if there was a statistically significant difference between the pharmacokinetic parameters following the treatments. No significant difference was seen for the parameters analysed by ANOVA ($P > 0.05$). No adverse events or clinical reactions were considered to be as a result of treatment.

It was concluded that bioequivalence was demonstrated for the test product with the reference product based on the data for this study. The pharmacokinetic parameters were measured and the 90% CI fell within the pre-defined limits, indicating no statistically significant difference between the test product and the reference product.

Tolerance in the Target Species of Animals

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of tolerance studies are not required.

Resistance

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, resistance data were not required. Relevant warnings are included on the SPC and product literature.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of clinical studies are not required.

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)