I. INTRODUCTION

Alomec, 18.7 mg/g Oral Paste is an endectocide for use in horses and ponies. This product contains the active substance ivermectin and is indicated for the treatment of a variety of parasitic infections. Target parasites include the following: Large strongyles, *Strongylus vulgaris* (adult and arterial larval stages*), S. edentatus* (adult and tissue larval stages), *S. equinus* (adult), *Tridontophorus brevicauda* and *Tridontophorus serratus* (adult), and *Craterstomum acuticaudatum* (adults). In addition, Alomec, 18.7 mg/g Oral Paste may be used to treat numerous small strongyles, adult and immature forms. Target species also include three *Coronocyclus spp*, two *Cyathostomum spp*, six *Cylicocyclus spp*, six *Cylicostephanus spp*, and a small number *of Gyalocephalus*, *Parapoteriostomum*, *Petrovinema* and *Poteriostomum* spp. This product may also be used to treat specific lungworms, pinworms, ascarids, large-mouthed stomach worms, neck threadworms, intestinal threadworms and stomach bots.

Alomec, 18.7 mg/g Oral Paste is a yellow gel-like paste for oral administration, containing 1.87% w/w ivermectin. The product is presented in a dial-a-dose syringe. This abridged application was made under Article 13 (1) of Directive 2001/82/EC as amended and is a generic application using Eqvalan Paste for Horses 1.87% w/w as the reference product.

II. QUALITY ASPECTS

Product Development and Composition

The production site for the active manufacturer conforms to Good Manufacturing Practise (GMP) and satisfactory Manufacturing Authorisations were provided for the preparation of the product.

Active Substance

The active substance in this product is ivermectin, monographed in the European Pharmacopoeia (Ph. Eur). An appropriate certificate of suitability (CEP) was provided and the product is prepared to given specifications. Confirmation that the active substance is prepared to specification is provided via batch analyses, data for which comprised results of tests from three full-scale production batches. The results were satisfactory.

Other Substances

The excipients in Alomec, 18.7 mg/g Oral Paste are apple flavour, polysorbate 80, colloidal anhydrous silica and refined maize oil. All excipients except the apple flavour are monographed in the Ph. Eur. Polysorbate 80 and colloidal silica are analysed for appearance, solubility and identification. The apple flavour is controlled by an in-house specification which consists of the description, identification, specific gravity, solubility and refractive index of this excipient.

Packaging Materials

This product is presented in a multi-dose oral syringe, on which the dose may be adjusted. The syringe barrel and multi-dose slide ring are formed of a high density polyethylene, the cap and plunger seal are formed from low density polyethylene. The raw materials conform to the relevant Ph. Eur requirements and visual and infra-red examinations are carried out by the applicant on receipt of the products.

Manufacture of the Finished Product

The manufacture of the finished product comprises of a step-wise addition and mixing process. Maize oil and polysorbate 80 are mixed and the apple flavour added, ivermectin is then added. Silica is added after further mixing and then the paste is filtered before being inserted into syringes. Three batches of product were analysed for air retention within the syringe, it did not occur. The process was validated for bulk preparation of this product.

Finished Product Quality Control

Tests and associated limits were satisfactory. Alomec, 18.7 mg/g Oral Paste is tested for syringeability, viscosity, related compounds and expelled weight, total viable cell count and the presence of *Escherichia coli*. An HPLC assay is performed which tests for accuracy, precision, linearity, range, robustness and ivermectin specificity. All tests conform to satisfactory procedural methods.

Batch analyses were presented for four 100 kg and three 400 kg pilot batches. The data was satisfactory.

Stability of the Product

Active substance

The CEP for the active substance stated that the retest period for ivermectin was thirty-six months when stored in a double-lined polyethylene heat-sealed bag in 1 kg aluminium tins. The storage temperature is restricted to below 25^{o}C.

Finished Product

Stability studies on the finished product showed no interaction between the paste and the packaging.

In-Use

The shelf-life of the product as packaged for sale is two years and the product should be protected from light.

CONCLUSIONS ON QUALITY

Satisfactory data were provided with regard to Quality and the application for a Marketing Authorisation was supported.

III. SAFETY ASPECTS

Introduction

Alomec, 18.7 mg/g Oral Paste is a generic product, essentially similar to Eqvalan Paste for Horses. Two bioequivalence studies were submitted in support of this application.

Pharmacology

Pharmacodynamics

As this was a generic application made in accordance with Directive 2001/82/EC, data on pharmacodynamics were not required.

Pharmacokinetics

Two bioequivalence studies were submitted. These were two-way single-dose studies, conducted in horses with Eqvalan Paste for Horses. Details are given in Part IV of this report. Ivermectin is eliminated primarily via the faeces, and the highest residue levels are found in fat. At a dose rate of 0.2 mg ivermectin per kilogram of bodyweight, plasma levels of ivermectin reach a mean C_{max} concentration of 40.44 ng/ml and a mean T_{max} at 8.35 hours. This peak falls off gradually to an average level of 3 ng/ml at 10 days.

Toxicology

As this was a generic application made in accordance with Directive 2001/82/EC, data on toxicological studies were not required.

Residues

As this was a generic application made in accordance with Directive 2001/82/EC, data on residue depletion studies were not required.

Maximum Residue Limits

Ivermectin is contraindicated in animals intended for human consumption. Excipients polysorbate 80 and colloidal anhydrous silica have entries in Annex II of Regulation 2377/90. Data on excipients were permissible.

Environmental Safety

Alomec, 18.7 mg/g Oral Paste is a generic of the reference product Eqvalan Oral Paste for Horses, therefore the authorised acceptance of Eqvalan Paste on environmental grounds was pertinent to the granting of a Marketing Authorisation for Alomec.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The following instructions are included in the SPC:

Do not smoke, drink or eat 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

Conclusions on Consumer Safety

The withdrawal period for Alomec, 18.7 mg/g Oral Paste is twenty-one days for meat and offal. Animals must not be slaughtered for human consumption during treatment and the product must not be used in animals producing milk for human consumption.

Conclusions on Environmental Safety

This product is safe for the environment when used as directed.

IV. CLINICAL ASPECTS

Introduction

This application for a Marketing Authorisation was granted as essential similarity was demonstrated with the pioneer product, Eqvalan Oral Paste for Horses. The claim for essential similarity was based on two bioequivalence studies carried out in the target species.

Clinical Pharmacology

Pharmacodynamics

Ivermectin is a member of the macrocyclic lactone group of endectocides. The compound binds selectively to the glutamate-gated chloride ion channels present in invertebrate nerve and muscle cells. The resulting death of the parasite is caused by the increase in the permeability of the invertebrate cell membrane to chloride ions and the subsequent hyperpolarisation of the nerve or muscle cell. Ivermectin is targeted only to the parasite because mammals do not possess glutamate-gated chloride ion channels and there is only low affinity to other ligand-gated chloride ion channels that are found in the mammalian system.

Pharmacokinetics

Ivermectin is rapidly absorbed by the horse following administration of Alomec, 18.7 mg/g Oral Paste, with peak plasma levels being attained in several hours. The peak plasma level falls over several days following administration. Elimination of ivermectin is primarily via the faeces, the highest residue levels being found in fat.

Two Good Laboratory Practice (GLP) bioequivalence studies were presented by the applicant in order to show that Alomec, 18.7 mg/g Oral Paste was essentially similar to Eqvalan Oral Paste for Horses. In the first study, a two-way, single-dose blood level bioequivalence study was performed. A suitable number of horses of differing ages and weights were acclimatised prior to the commencement of the study. None of the horses had been pre-treated with avermectin or milbimycin prior to the study and all animals were healthy. The animals were paired up for a cross-over study on the basis of bodyweight and type. Each animal was randomly assigned to one of two treatment groups, the treatments being swapped after a suitable wash-out interval. Animals were administered treatments on days one and forty-two of the trial period, both products being administered orally via syringe. The horses were subjected to clinical examination on various days during the trial. The animals were also observed twelve and forty-eight hours directly after treatment. The dose rate was 200 µg ivermectin per kg bodyweight. Blood samples were taken at various timepoints and assayed for ivermectin B1a using HPLC. The Limit of Quantitation (LOQ) was 0.250 ng/ml and the Limit of Detection (LOD) was 0.071 ng/ml. Those administering the treatments to the animals did not know which product was being given, and the horses were examined periodically during the trial for intolerance to the products.

No adverse effects due to the administration of products was noted, and no significant difference was seen statistically when AUC, C_{max} and T_{max} were analysed using the Student's 't' test, providing proof that the test and reference products were directly comparable. 90% confidence limits for log-transformed data for AUC and C_{max} in addition to the ratio of AUC for the test and reference products contributed to the positive assessment.

A second study supported the results of the first study. The objective was to analyse the test product in comparison with the reference product Eqvalan Oral Paste for Horses. A number of horses were acclimatised several days before the commencement of the study before being divided into pairs for the two-way single-dose trial began. All animals were in good health and had not received any drug treatment prior to the start. The horses were weighed and observed at various timepoints. Before and after administration of the products, blood samples were taken regularly and assayed for ivermectin B1a and B1b using HPLC. The LOQ was 0.50 ng/ml and 1.41 respectively for B1a and B1b, and the corresponding LODs were 0.0625 ng/ul and 0.10 ng/ul. A wash-out period was utilised whereby the two drugs used in the trial were swapped between two animals after the testing of the first product. No adverse reactions due to the treatments were noted in the trial. Ensuing analyses measured ivermectin B1a and total ivermectin. 90% confidence intervals for $AUC_{0\text{-}LOQ}$ for both B1a and total ivermectin were shown to be within acceptable limits for confirming essential similarity between then test and reference products.

Tolerance in the Target Species

As this was a generic application in accordance with Article 13 (a)(iii) of Directive 2001/82/EC, no target species tolerance studies were required with regard to the active component. With regard to the excipients, all are standard apart from the apple flavour, which has its own acceptable in-house specification.

Resistance

In accordance with Article 13 (a)(iii) of Directive 2001/82/EC, no data on resistance to ivermectin were required for the original application. Under a Renewal Procedure in 2014, the section of the SPC relating to resistance was updated, and states the following:

- Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:

- Too frequent and repeated use of anthelmintics from the same class, over an extended period of time.

- Underdosing, which may be due to underestimation of body weight, misadministration of the product, or lack of calibration of the dosing device.

- Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Test). Where the results of the test (s) strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used.

- Resistance to macrocyclic lactones (which includes ivermectin) has been reported in Parascaris equorum in horses in a number of countries within the EU. Therefore, the use of this product should be based on local (regional, farm) epidemiological information about susceptibility of gastro-intestinal nematodes and recommendations on how to limit further selection for resistance to anthelmintics.

Clinical Efficacy

In accordance with Article 13 (a)(iii) of Directive 2001/82/EC, no specific data on efficacy were required

CONCLUSIONS ON CLINICAL ASPECTS

Alomec, 18.7 mg/g Oral Paste is bioequivalent to Eqvalan Oral Paste for Horses. Although excipients in the test and reference products differ, the excipients in the test product contain no pharmacological activity. This in combination with the fact that this product is an oral presentation meant that specific tolerance studies were not required.

PART V. OVERALL CONCLUSION ON THE PRODUCT

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.

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)