I. INTRODUCTION

Paramectin Drench 0.08% w/v Oral Solution is an endectocide and contains the active substance ivermectin (a drug that expels parasitic worms from the body and kills external parasites such as lice). The product is authorised to be used in sheep for the treatment and control of gastrointestinal nematodes, lungworms, and nasal bots. These parasites cause damage to animals leading to loss of condition, suffering and possibly death.

- Lungworm cause inflammation and irritation to the lungs, leading to coughing, difficulty in breathing and in severe cases can lead to death.
- Roundworms live in the gut, causing damage to the gastro-intestinal tract which can result in diarrhoea and reduced nutrient intake and utilisation.
- Nasal bots live in the nasal passages and can result in extreme irritation during larva positioning, and later, during larval development, a mucoid and sometimes bloody nasal discharge, loss of appetite, vigorous head shaking, secondary infection of the sinuses and sometimes death can occur.

Paramectin Drench 0.08 w/v Oral Solution should be administered at a dosage rate of 200µg per kg bodyweight (2.5ml per 10kg bodyweight). It should be administered orally, and it is recommended that a suitably calibrated dosing gun is used to allow accurate dosing especially in young animals.

The product should not be used in sheep that produce milk for human consumption.

The application for a Marketing Authorisation for Paramectin Drench 0.08% w/v Oral Solution was made on the basis of its essential similarity[1] to the established product Oramec Drench (Authorisation Number Vm 08327/4191), first authorised in February 1994 and marketed in the UK by Merial Animal Health. For this type of application, companies are exempted from the usual requirement to produce evidence of safety and efficacy, if they show that the composition of the proposed product is essentially similar to, i.e. closely resembles, that of an established product, i.e. one authorised in the EU for more than 10 years.

II. QUALITY ASPECTS

Product Development and Composition

The product is supplied in 1 litre, 2.5 litre and 5 litre packs, and in addition a two 5 litre pack. The volumes and development of the formulation have been justified.

Active Substance

Ivermectin

The active substance complies with the relevant requirements of the European Pharmacopoeia.

Other Substances

Polysorbate 80
Dimethlacetamide
Benzyl Alcohol

[1] This means that the application was made under the provisions of Article 13.1.a.iii of Directive 2001/82/EC.

Sodium Phosphate Dihydrate
Sodium Acid Phosphate Dihydrate
Water Purified

All the substances listed above comply with the requirements of the relevant European Pharmacopoeial monographs.

Packaging Materials

Paramectin Drench 0.08% w/v Oral Solution is supplied in high density polyethylene (HDPE) jerricans or rigid back packs with polypropylene closures. The backpacks have been tested inverted with a representative group of dosing equipment and no evidence of leakage was apparent. All materials comply with the requirements of the appropriate European Pharmacopoeia monographs.

Manufacture of the Finished Product

All production steps are performed according to pharmaceutical Good Manufacturing Practice (GMP), using conventional techniques. The validation of the process was carried out on three batches of Paramectin Drench 0.08% w/v Oral Solution. The studies conducted demonstrate that the solution can be produced to a consistent and appropriate quality.

All components of the product have been demonstrated to comply with relevant guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

Finished Product Quality Control

The specification for the finished product controls appropriate parameters, including appearance, pH[2], specific gravity, fill volume and microbial purity. Also the identity, content and total amount of ivermectin and the identity, content, and total amount benzyl alcohol were tested for. Data have been provided which demonstrate the suitability of the methods used for testing the product.

Stability of the Product

Active substance

A retest period of three years has been demonstrated when the active substance is stored in a double-lined polyethylene, heat-sealed bag, stored within an aluminium can.

Finished Product

The company provided data on three batches of the oral solution after storage in white, one litre HDPE jerricans or rigid backpacks with polypropylene closures under standard conditions of temperature and humidity. Tests conducted on the oral solution stored in this way demonstrated that the product still meets the agreed specification after 5 years.

[2] Is an indicator of acidity.

CONCLUSIONS ON QUALITY

The supporting data submitted by the company demonstrate that the oral solution is suitably formulated and quality-controlled. A shelf-life of 5 years is justified for the solution supplied in HDPE jerricans and rigid backpacks subject to the following storage warnings.

Do not store above 25°C.

III. SAFETY ASPECTS

Introduction

The application for Paramectin Drench 0.08% w/v Oral solution is based on essential similarity to the established product Oramec Drench, by Merial Animal Health Ltd. It is an aqueous solution containing 0.08% ivermectin and is for oral administration to sheep.

Pharmacology

This application is based on essential similarity; therefore the company is not required to present information on pharmacodynamics.

Pharmacokinetics is discussed in the efficacy section of this report.

Toxicology

This application is based on essential similarity; therefore the company is not required to present information on toxicology.

Residues

The company has submitted a residues study and this showed that at 10, 14 and 18 days post treatment there were no residues detectable above the limit of quantification of 7.5µg in any tissues. Although it is not necessary to submit any residues studies for this type of application, this supports the withdrawal period.

Ivermectin is in Annex I of Regulation 2377/90 as amended by 869/2005, which means that Maximum Residue Limits (MRLs) have been established for these substances for the protection of public health. All the excipients are in Annex II, which means that it is not considered necessary to set MRLs to protect public health.

The essentially similar product has a withdrawal period of 14 days for meat, and therefore based on this and the information above, Paramectin Drench 0.08% w/v Oral Solution has the same withdrawal period. It is now a condition that ivermectin products are contraindicated for use in animals producing milk for human consumption. Therefore this is contraindicated on the SPC[3].

Withdrawal period Sheep (meat and oral) 14 days Do not use in sheep producing milk for human consumption

[3] Summary of Product Characteristics

Environmental Safety

The company provided an environmental risk assessment. As Paramectin Drench 0.08% w/v Oral Solution is essentially similar to Paramectin Drench and will be used in the same way, then the same environmental warnings can be applied.

They are listed in the SPC[3] as the following;

EXTREMELY DANGEROUS to fish and aquatic life do not contaminate ponds, waterways or ditches with the product or unused container. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

Ivermectin is also authorised for use in humans in the medicinal management of onchocerciasis[4], and is administered orally.

The user exposure is thought to be mainly through skin contact or (deliberate) ingestion. Due to the formulation of the product, exposure through inhalation is limited. As this is an 'essentially similar' application, the user warnings that are used for the essentially similar product can be applied to Paramectin Drench 0.08% w/v oral solution, without the need for the company to submit a full user risk assessment.

These warnings are stated on the SPC[3].

Do not smoke, drink or eat while handling the product. Wash hands after use. Avoid contact with skin and eyes. In case of accidental spillage onto the skin or eyes, wash the affected area with clean running water immediately. Seek medical attention if irritation persists.

Conclusions on Consumer Safety

There are no consumer safety concerns.

Conclusions on Environmental Safety

The data provided by the company have demonstrated that the warnings on the SPC[3] are satisfactory to limit environmental exposure of ivermectin.

[4] A parasitic worm that can live in the human body and cause blindness.

IV. CLINICAL ASPECTS

Introduction

The application for Paramectin Drench 0.08% w/v Oral Solution is based on essential similarity to the established product Oramec Drench, by Merial Animal Health Ltd. It is for use as an endectocide against adult and immature gastrointestinal nematodes, adult and immature lungworms and all larval stages of nasal bots in sheep. All the studies discussed below were conducted in accordance with GLP[5].

Clinical Pharmacology

Pharmacodynamics

This application is based on essential similarity; therefore the company is not required to present information on pharmacodynamics. However, the company has provided some additional information for this section.

Ivermectin is believed to be adsorbed via the cuticle in most nematode species, and ingestion is also an important route of uptake in most species of nematode and ectoparasite that feeds on blood. The mode of action of ivermectin is widely described in literature.

Pharmacokinetics

The pharmacokinetic behaviour of ivermectin depends on the formulation, species of animals and route of administration. It is known to be adsorbed systematically when given by oral and dermal routes, as well as by injection.

The formulations of Paramectin Drench 0.08% w/v Oral Solution and Oramec Drench are essentially similar, and their bioequivalence has been demonstrated in the following study.

The study was of a cross-over design with a single administration in each of the two periods of the study. The animals were split into two groups and one group received Paramectin 0.08% w/v Oral Solution and the other Oramec Drench. The objective of the study was to compare levels of ivermectin in animal's plasma following an oral administration of Paramectin Drench 0.08% w/v Oral Solution and Oramec Drench. All test animals were weighed one day and 20 days before each dosing period. The products were administered by a drenching nozzle attached to a syringe, and a separate one was used per product. Both products were administered at a rate of 200µg ivermectin/kg bodyweight.

Blood samples were obtained and the plasma was tested to determine the levels of ivermectin present. After administration of the products the animals were observed twice daily for changes in their general health. Animals were also individually examined twice a week throughout the two dosing periods for evidence of adverse reactions to the treatments. At the end of the second period tissue samples were obtained from the two groups to determine the levels of ivermectin present.

The data showed that Paramectin Drench 0.08% w/v Oral Solution demonstrated similar bioavailability to Oramec Drench, and that overall the two products can be considered bioequivalent.

[5] Good Laboratory Practice

The one adverse effect observed in the study was that after treatment some sheep were heard to cough. This is a common occurrence following drenching and a warning has been included on the SPC[3] to reflect this.

Some animals may cough slightly immediately after treatment. This is a temporary occurrence and is of no clinical consequence.

Tolerance in the Target Species

As Paramectin Drench 0.08% w/v Oral Solution has different excipients to Oramec Drench, the company provided a target species tolerance study.

The animals were split into 3 groups; one group received a single recommended dose of the product, one group received a double dose of the product and one group was left as untreated controls. All treatments were administered orally once.

Each animal was monitored daily prior to and until 18 days after treatment. During the study blood samples were obtained, bodyweight was recorded and physical examinations were conducted. Residue analysis also took place.

The study showed that the animals that were given a double dose did not gain weight as well as animals that only received a single dose. Other than this no significant differences were observed and the doses were well tolerated by the animals. No treatment related adverse physical effects were noted.

Resistance

This application is based on essential similarity; therefore the company is not required to present information on resistance.

Clinical Efficacy

This application is based on essential similarity; therefore the company is not required to present information on clinical efficacy.

CONCLUSIONS ON CLINICAL ASPECTS

The company provided a bioequivalence study, which showed that the two products were bioequivalent, due to Paramectin Drench 0.08% w/v Oral solution not having the same excipients as Oramec Drench. The company conducted a target species tolerance study which showed that the product has an adequate safety margin in practice when used in the target animal.

It is considered that the company has shown that Paramectin Drench 0.08% Oral Solution and Oramec Drench are essentially similar. Therefore it is considered that the same claims and warnings can be accepted for Paramectin Drench 0.08% w/v Oral Solution as are on the SPC[3] for Oramec Drench.

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 risk benefit 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)