I. INTRODUCTION

Triclafas Drench 5% w/v Oral Suspension is a suspension of triclabendazole for administration by mouth. It is used for the specific treatment and control of the liver fluke (*Fasciola hepatica*) infections in sheep. *Fasciola hepatica* is a parasite which spends some of its life cycle in sheep or cattle and some in a particular type of snail. The disease is common in ruminants, particularly in wet areas, and can be fatal. It can be difficult to eradicate because even when the sheep have been treated, some of the parasites may remain in the snails and then re-infest the sheep.

Triclabendazole belongs to a group of substances known as benzimidazoles. Although it is not known exactly how these substances work, it is thought that they interfere with the parasites' metabolic processes. Triclabendazole is effective against immature and adult stages of the parasite. Triclabendazole has also been used as a human medicine.

The recommended dose is 10 mg Triclabendazole per kilogram bodyweight i.e. 1 ml of the product per 5 kg bodyweight.

The application for a Marketing Authorisation for Triclafas Drench 5% w/v Oral Suspension was made on the basis of its essential similarity[*] to the established product Fasinex 5% (Vm 12501/4018), first authorised in January 1984 and marketed in the UK by Novartis Animal Health UK Ltd. For this type of application, applicants 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 a suspension, appropriately presented in 1 litre, 2.5 litre or 5 litre white, opaque, high density, flat bottomed polyethylene flexipacks with white polypropylene screw fit cap and induction seal.

In addition to triclabendazole at 50 mg per ml, the suspension contains as preservatives propyl parahydroxybenzoate at 0.4 mg per ml and methyl parahydroxybenzoate at 1.1 mg per ml.

Other ingredients are:

Microcrystalline cellulose and carmellose sodium (89:11 ratio)
Povidone K30
Sodium phosphate Dihydrate
Simethicone
Phosphoric acid 85% w/w (for pH adjustment)
Purified Water

Active Substance

Information on the manufacture and control of the active ingredient has been presented by its manufacturer. There is no European Pharmacopoeia monograph for triclabendazole and Norbrook Laboratories Ltd therefore requires compliance of the active ingredient with its own

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

specification. The limits for impurities comply with current international guidelines and the limits on particle size are defined by the particle size of triclabendazole in batches of product used in studies submitted in the application dossier.

Other Ingredients

These comply with the tests specified in the relevant monograph of the European, US or British Pharmacopoeia.

Packaging Materials

Components of the polyethylene flexi packs comply with the relevant pharmacopoeial monographs. The thickness of the pack itself and the material that is actually in contact with the product is suitably controlled, and similar assurances have been provided for the materials used in the heat seals and screw caps.

Manufacture of the Product

The product is manufactured in accordance with GMP*. The manufacturing process has been described in some detail and is considered appropriate for a suspension designed for the treatment of liver fluke. The process involves adding the ingredients in a specified order with appropriate mixing to produce a homogeneous suspension of triclabendazole. Phosphoric acid is added towards the end of the procedure to ensure that the correct pH (degree of acidity) is achieved. Appropriate checks are made at various stages of the process, and data have been submitted on several batches of the product to show that the process consistently produces a homogeneous product, and that it does not induce degradation of the active ingredient.

Finished Product Quality Control

The specification for the finished product contains tests and limits for appearance, pH, viscosity, particle size of suspended triclabendazole, identification and assay of active ingredient and preservatives, efficacy of the antimicrobial preservative and uniformity of dose dispensing from a standard drenching “gun”. The range of tests is appropriate to the type of product, and data have been provided to demonstrate the suitability of the testing methods.

Data have also been provided showing that a product can be produced that meets this specification.

Stability of the product

Active substance

Satisfactory stability data were submitted on three batches of the active substances, justifying a shelf-life of 12 months.

Finished Product

Stability studies have been performed on six batches of the product. Samples of these batches were stored in the smallest and largest of the approved packs, and subjected to accelerated testing and to long-term testing under standard test conditions.

* GMP = Good Manufacturing Practice

In-Use
Data on stability of the product once the pack has been opened are not required for a product that is to be administered by mouth.

CONCLUSIONS ON QUALITY

The data submitted by the company demonstrate that Triclafas Drench 5% w/v Oral Suspension is suitably formulated and quality-controlled. Data show that it is essentially similar to the established product Fasinex 5%. A shelf-life of 24 months is justified subject to the following storage warnings:

- Do not store above 25°C.
- Protect from freezing.

III. SAFETY ASPECTS

The application was based on essential similarity of Triclafas Drench 5% w/v Oral Suspension to the established product Fasinex 5%. The company demonstrated that the products were essentially similar by submitting the report of a bioequivalence study, that is a study which compared the two products in terms of how much of the active ingredient, triclabendazole, was absorbed into the bloodstream when the products were given as recommended, i.e. by mouth. This study is described below.

The study utilised a well-accepted study design known as a “crossover” design, and involved two groups of sheep. The first group received Triclafas Drench 5% w/v Oral Suspension at the recommended dose; after a suitable delay to allow all the triclabendazole to disappear from their systems, they received Fasinex 5%, again at the recommended dose. The second group of animals were treated in the same way except that they received Fasinex 5% first, and Triclafas Drench 5% w/v Oral Suspension second, hence the term “crossover”. Blood samples were collected from all the sheep at intervals throughout the study and the amount of triclabendazole* in these samples was measured. When all the measurements had been collected, a graph of the amounts at the different times was produced. From this it was possible to see that the amount of triclabendazole that had reached the bloodstream was similar for both products. This was confirmed by a statistical analysis of the data.

The company had therefore demonstrated that Triclafas Drench 5% w/v Oral Suspension complied with the official definition of essential similarity. This means that no further information was required to demonstrate the safety of the product for man or the environment.

Although not strictly necessary, the company also provided a study in which the amount of triclabendazole or its metabolites in the edible parts of the sheep was measured. Under the rules for essentially similar products, the withdrawal period for Triclafas Drench 5% w/v Oral Suspension may not be less than the withdrawal period for the established product, Fasinex 5%. The results of the study submitted by the company confirmed that the 56-day meat withdrawal period which applies to Fasinex 5%, when applied to Triclafas Drench 5% w/v Oral Suspension, will be adequate to ensure consumer safety.

* Triclabendazole is converted to various other substances, called metabolites, once it enters an animal’s body, and it is therefore the amount of these substances that is actually measured, not triclabendazole itself.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The applicant submitted a user risk assessment that concluded, appropriately, that because Triclafas Drench 5% w/v Oral Suspension and Fasinex 5% are essentially similar, any risk to users of the products would be the same. Hence the user warnings that had already been approved for Fasinex 5% are also appropriate for Triclafas Drench 5% w/v Oral Suspension. These warnings are as follows:

- When using, do not eat, drink or smoke.
- Wash splashes from eyes and skin immediately.
- Take off immediately any contaminated clothing.
- Wash hands and exposed skin before meals and after work.

Conclusions on Consumer Safety

The following withdrawal period is acceptable:

Sheep (meat & offal) – 56 days
Do not administer to sheep producing milk intended for human consumption.

Conclusions on Environmental Safety

Because the application was made on the basis of essential similarity to an established product, it is exempt from the requirement for ecotoxicity testing because environmental safety aspects of the established product have already been considered. Ecotoxicity data were not required for this type of product (Generic/Essentially similar) when the application was accepted by the VMD.

Disposal advice is the same for the two products:

“Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority. Do not contaminate ponds, waterways or ditches with the product or used container”

PART IV. CLINICAL ASPECTS

The application was based on essential similarity of Triclafas Drench 5% w/v Oral Suspension to the established product Fasinex 5%. The company demonstrated that the products were essentially similar by submitting the report of a bioequivalence study, that is a study which compared the two products in terms of how much of the active ingredient, triclabendazole, was absorbed into the bloodstream when the products were given as recommended, i.e. by mouth. This study was described in Part III of this report.

The study demonstrated that Triclafas Drench 5% w/v Oral Suspension complied with the official definition of essential similarity. This means that no further information was required to demonstrate the efficacy of the product or its safety for sheep.

Although not strictly necessary, the company also provided the report of a study of the effects of Triclafas Drench 5% w/v Oral Suspension on sheep. In this study, sheep were given the product at either the recommended dose, but on two consecutive days, or five times the

recommended dose, also on two consecutive days. This was to find out what might happen if someone accidentally overdosed their sheep or dosed them twice instead of once. Some sheep were given the product without any of the active ingredient. The animals were observed for an hour after treatment to see if any unusual signs appeared, and their heart rate and temperature was checked. Blood samples were collected and a full range of tests were made on these samples to see if there were any changes in the biochemical composition of the blood or in its cells.

One or two small changes were noticed in this study but the company demonstrated that these were not serious enough to cause concern for sheep treated in the recommended manner, or even those accidentally overdosed.

CONCLUSIONS ON CLINICAL ASPECTS

The company demonstrated that Triclafas Drench 5% w/v Oral Suspension is essentially similar to the established product Fasinex 5% and provided some additional data which provided further re-assurance about the product's safety.

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 man 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)