I. INTRODUCTION

This product has been authorised as an Extension to the existing national marketing authorisation for Fasinex 10 %, adding a new strength of product. Fasinex 240, 24% Oral suspension is an oral suspension containing triclabendazole 240 mg/ml for use in the treatment of acute, subacute and chronic infection due to early immature, immature, and mature stages of *Fasciola hepatica.* The recommended dose rate is 5 ml per 100 kg bodyweight. The new strength of formulation has been justified on the grounds of a dose volume which is easier to calculate and easier to administer to the animal.

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 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

Product Development and Composition

The product contains the active substance triclabendazole and the excipients methyl hydroxybenzoate, propyl hydroxybenzoate, benzyl alcohol, microcrystalline cellulose and carmellose sodium, povidone, simethicone emulsion, propylene glycol and purified water.
The product is packaged in high density polyethylene flexipacks of 0.8, 2.2 and 5.0 litres with a polypropylene flip-top cap or a high density polyethylene bottle of 12.0 litres with screw-fit cap. The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the formulation and presence of preservative have been justified.
The product is an established pharmaceutical form and its development has been adequately described in accordance with the relevant European guidelines.

Active Substance

The active substance is triclabendazole. No pharmacopoeial specification is available for triclabendazole, for which an in-house specification has been developed. 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.

Other Substances

Dispersible Cellulose, an intimate mixture of microcrystalline cellulose and carmellose sodium, is the subject of a monograph in the British Pharmacopoeia. All other ingredients are described in the European Pharmacopoeia. The specifications applied are appropriately those of the relevant monograph. The dossier includes a certificate of analysis for one batch of each ingredient, showing compliance.

Packaging Materials

Each size of container for the product is required to be accompanied by the supplier's certificate of compliance with the agreed specifications, including identity and suitability for food use in accordance with directive 2002/72/EC. Testing is considered adequate and appropriate. A specimen certificate of analysis showing compliance has been presented for each component.

Manufacture of the Finished 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.
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

Finished Product Quality Control

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.
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.

Stability of the Product

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.
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.
A shelf life of 3 years and in-use shelf-life of 12 months has been considered justified under the appropriate storage conditions.

CONCLUSIONS ON QUALITY

The product is appropriately formulated and controlled. A shelf-life of three years in unopened container has been justified. An in-use shelf life of 12 months was also justified. No restrictions on the temperature of storage of the product are necessary, nor is the product susceptible to light or frost. The warning “Store in tightly closed original container” is a sensible precaution. Advice in SPC specifies administration 'after thorough shaking of the suspension'. This is reflected on the product labels by the warning “Shake thoroughly before use”.

III. SAFETY ASPECTS

Pharmacology

Reference has been made to the data that was submitted in support of the original Fasinex 5% product. The applicant also submitted a number of in-house studies.
The mode of action of triclabendazole is not fully clear but the active is thought to interfere with intracellular transport mechanisms and inhibit protein synthesis. It is active against the liver fluke *Fasciola*.
Studies in the rat, dog, sheep, goat and rabbit demonstrated that the majority of an oral dose of triclabendazole was eliminated in the faeces with minimal urinary excretion. In all species tested (sheep, cattle, goats and rats) the same metabolites of triclabendazole were found in the faeces but in different proportions.
Appropriate information regarding pharmacodynamics and pharmacokinetics is reflected in the SPC.

Toxicology

Single dose toxicity

Triclabendazole was shown to be of low acute toxicity when administered by the oral, intraperitoneal, dermal and inhalation routes in rats and mice, oral LD_{50} values being in excess of 8000 mg/kg and the intraperitoneal LD_{50} in the rat being 1666 mg/kg. However, the oral LD_{50} value in the rabbit was 206 mg/kg. The sulphoxide and sulphone metabolites of triclabendazole also had low acute oral toxicity. Triclabendazole produced minimal skin irritation and no eye irritation in the rabbit. An optimisation test in the guinea pig produced sensitisation on intradermal challenge but not on epidermal exposure.

Repeated dose toxicity

Repeated-dose toxicity studies in rats fed diets containing 10, 100 or 1000 mg/kg feed triclabendazole revealed minor transient haematological effects and some effects on clinical chemistry at high doses (equal or greater than 100 mg/kg feed). Decreased food intake and growth retardation were observed at 1000 mg/kg feed. No effects were seen at 10 mg/kg feed (NOEL = 0.7 mg/kg bw). A 13-week feeding study in dogs (10, 100 or 1000 mg/kg feed triclabendazole) revealed slight hepatotoxicity, growth retardation, delayed onset of sexual maturity, reversible electrocardiogram changes and haemolysis at 1000 mg/kg feed. Elevated alkaline phosphatase was also seen at 100 mg/kg feed. The NOEL was 10 mg/kg feed (0.35 mg/kg bw).

Reproductive toxicity (including teratogenicity)

In a two-generation study in rats, animals were exposed to dietary levels of 3, 15 and 75 mg/kg feed triclabendazole. A NOEL was determined at 3 mg/kg feed (0.15 mg/kg bw/day).

In a number of teratogenicity studies in rats the overall NOEL for these studies was 50 mg/kg bw. In a teratogenicity study in rabbits exposed to doses of 3, 10 and 20 mg/kg on gestation days 6-18 the NOEL was 3 mg/kg bw. Oral administration to sheep of single or multiple doses of 10-50 mg/kg bw had no adverse effects on reproductive parameters or offspring. However, oral administration to pregnant ewes in combination with fenbendazole at high doses (single doses of 150 mg/kg bw of a 1:1 mixture on day 12, 17, 21 or 28) caused kidney and skeletal abnormalities in some offspring of ewes exposed on days 12 or 21. In cattle, doses of 15-30 mg/kg bw during the first or 2-7 months of pregnancy caused no adverse effects. Single or four weekly oral doses of 50 mg/kg bw had no effect on testis weights or sperm concentration or quality in male sheep.

Mutagenicity

A number of i*n vitro* and *in vivo* mutagenicity tests indicated that triclabendazole is not a mutanegenic.

Carcinogenicity

A number of carcinogenic studies were conducted. A carcinogenicity study was conducted in mice where the only pathological findings were increased serum levels of hepatic enzymes, increased liver-weight and benign hepatomas in females in the highest dose group only (300 mg/kg in the diet).

A chronic toxicity/carcinogenicity study conducted in mice (3, 15, 60 or 300 mg/kg feed triclabendazole in the diet for 737-752 days) showed a NOEL of 60 mg/kg feed (5.35 mg/kg bw).

A well-conducted chronic toxicity/carcinogenicity study in rats (3, 13, 30 or 100 mg/kg in the diet for 2 years) showed a NOEL of 30 mg/kg feed (equivalent to about 1.5 mg/kg bw/day).

Studies of Other Effects

Observations in humans

Triclabendazole is been used in clinical trials for the treatment of parasitic infestations in humans. Single and double doses of 10 mg/kg bw were well tolerated. Transient epigastric pain was attributed to the death of the parasites.

Preliminary studies in humans indicate that triclabendazole is well absorbed from the gut. In fasted patients, peak plasma levels occurred 2 hours after a single oral dose of 10 mg/kg bw. Administration after a meal resulted in plasma levels approximately 3 times higher those in fasted subjects. The sulphoxide and sulphone metabolites were identified in plasma, with the sulphoxide predominating. Parent compound was undetectable after 8 hours, peak levels of the sulphoxide and sulphone were found at about 4 hours and were still present at low levels at 24 hours.

User Risk

The applicant provided a detailed user risk assessment of the product. The active substance is of low toxicity and the operator warnings are also in line with what has already been agreed with the other similar products.

- Do not eat, drink or smoke while handling the product.
- Wash hands and exposed skin before meals and after work.
- In case of accidental spillage onto skin or eyes, wash immediately with water. Take off any contaminated clothes.

These warnings and precautions are adequate to ensure safety to users of the product.

Residues

The applicant made reference to the residues data that were submitted in support of Fasinex 10% Oral Suspension for Sheep.

The applicant has provided a residue study in cattle following repeated dose of Fasinex 10%. The animals were administered 1.5x more than the recommended dose (18 mg/kg instead of 12 mg/kg) and they were also administered the product again after 28 days. Results justified a withdrawal period of 52 days in meat. Milk for human consumption may only be taken 48 hours after calving. The product is not intended for use within 48 days of calving. If calving occurs before 48 days after treatment, milk for human consumption may only be taken from 50 days after treatment.

Environmental Safety

Direct entry of the active ingredient into the environment is unlikely and residues of triclabendazole will reach the soil environment directly in the excreta of treated cattle.

Metabolism data indicate that the primary route of excretion is via the faeces. Faecal residue consists of a number of metabolites including parent compound. Only 20% of the administered dose is excreted as triclabendazole. No metabolite in excreta represents more than 10% of the dose.

Triclabendazole has low solubility in water indicating that triclabendazole is likely to bind tightly to soil and can be classified as non-mobile. Leaching studies using soil columns have confirmed the low mobility of parent and metabolites in soil. The DT_{50} of triclabendazole in soil is 15 days which results in a classification of slightly persistent.

Using suitable exposure models, PEC[1] values were calculated for soil, dung, groundwater and surface water. Comparison of these PEC values with the data from acute effects studies indicates that there is an acceptable level of risk to both soil and aquatic organisms. A potential adverse effect to dung insects cannot be ruled out, however if such an adverse effect does occur it will be for a short period of time only. Overall the risk to dung insects is considered acceptable.

There are no concerns for groundwater from the use of the product. There are no concerns over the potential bioaccumulation of triclabendazole. The disposal advice on the SPC and literature is appropriate. The environmental safety of the product is acceptable.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety
The user risk assessment is detailed, and warnings and precautions are adequate to ensure safety to users of the product.

Conclusions on Consumer Safety
Results from a residue study in cattle justified a withdrawal period of 52 days in meat. The product should not be administered to cattle producing milk for human consumption or to dairy cows within 60 days of calving.

Conclusions on Environmental Safety
The disposal advice on the SPC and literature is appropriate. The environmental safety of the product is considered acceptable.

IV. EFFICACY

Clinical Pharmacology

Pharmacodynamics

The Applicant has stated that there are no new data to be submitted in this part of the dossier.

Pharmacokinetics

The product has been demonstrated to be super-bioavailable, compared to the reference product, by approximately 1.34 x. The bioequivalence guideline states “The decision that two or more products are bioequivalent should take into account not only the statistical significance of any numerical values, but also the medicinal significance of differences and intra and inter-subject variability. For certain products, greater variance in bioavailability can be tolerated because of the intended therapeutic use or because the product dose not require careful patient dosage regimen.” This indicates that this degree of super-bioavailability is acceptable in terms of efficacy, because the clinical effect on the parasite will be satisfactory.

[1] PEC=Predicted environmental concentration

Tolerance in the Target Species
The Applicant has not provided safety data relating to the final formulation of the product. The applicant has provided one reference which is evidence of the safety of triclabendazole in young cattle at doses up to 200 mg/kg which represents a 16.6 times overdose. A number of other supportive references have been provided. Triclabendazole has a well established use and a wide safety margin, and so this is acceptable in this instance. Local tolerance data has been extrapolated from the clinical trials and the dermal and ocular irritation / corrosion studies in rabbits. This is also acceptable.

Resistance
As it was accepted that the claim of “bio-equivalence” is valid, there remains no further requirement for the Applicant to provide further data relating to resistance.

Clinical Efficacy
As it was accepted that the claim of “bio-equivalence” is valid, there remains no further requirement for the Applicant to provide further data relating to clinical efficacy.

CONCLUSIONS ON EFFICACY
In summary, the applicant has demonstrated that the product is super bioavailable, and that the target animal safety profile of the product is such that this was acceptable for part IV of the dossier.

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)