ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fasinex 100 10% (w/v) Oral Suspension for Cattle and Sheep

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fasinex 100 10% (w/v) Oral Suspension for Cattle and Sheep
Applicant	Novartis Animal Health UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom
Active substance(s)	Triclabendazole
ATC Vetcode	QP52 AC01
Target species	Cattle and Sheep
Indication for use	**Cattle** For the treatment and control of liver fluke infections in cattle caused by all stages of triclabendazole-susceptible *Fasciola hepatica* from 2 week old immature to adult fluke. **Sheep** For the treatment and control of liver fluke infections in sheep caused by all stages of triclabendazole susceptible *Fasciola hepatica* from 2 day old immature to adult fluke.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Extension application in accordance with Article 39 (1) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

This product was previously authorised following an extension to a now expired national marketing authorisation for Fasinex 5 %, adding a new strength of product to become a 10% suspension, (Fasinex 100, 10% Oral Suspension for Sheep). The new strength of formulation was justified on the grounds of a revised dose volume which was easier to calculate and easier to administer to the animal. A further extension application has now been authorised for this product on 27 August 2010, in order to include a new species, cattle. Fasinex 100, 10% Oral Suspension for Cattle and Sheep is a suspension containing triclabendazole 10 mg/ml for use in the treatment and control of all stages of infections by liver fluke, *Fasciola hepatica*. The recommended dose rate for sheep is 1 ml per 10 kg bodyweight. The recommended dose rate for cattle is 3 ml per 25 kg bodyweight.

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

A. Composition

The product contains the active substance triclabendazole and the excipients methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), microcrystalline cellulose, disodium phosphate dodecahydrate (E339), polyvinyl pyrrolidone, benzoic acid (E210), croscarmellose solution and purified water.

The product is packaged in high density polyethylene bottles of 0.8, 2.2 and 5.0 litres with a polypropylene flip-top cap and in high density polyethylene bottles 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 is 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.

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 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.

All 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.

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.

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

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

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.
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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

A shelf life of 5 years and in-use shelf-life of 12 months is considered justified under the appropriate storage conditions: Protect from light. Protect from frost. Store in the tightly closed, original container.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

III.A Safety Testing

Pharmacological Studies

Previous to the recent extension application, reference was made to the toxicology data that was submitted in support of Fasinex 5% Oral Suspension for Sheep. Fasinex 5% Oral Suspension for Sheep was originally authorised in 1984. The following product, Fasinex 100, 10% Oral Suspension for sheep stated that the new formulation is identical to Fasinex 10%, a product authorised for the treatment of cattle. For the current extension data relating to two previous products, Fasinex 100, 10% Oral Suspension for Sheep and Fasinex 10% (for cattle, now expired) were presented.

A bioequivalence study was not required because the formulation is identical to that of the reference products and bioavailability of the reference products had already been demonstrated.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

Toxicological Studies

A toxicology study was not required because the formulation is identical to that of the reference products and bioavailability of the reference products had already been demonstrated.

User Safety

The active substance is of low toxicity and the same operator warnings as designated for the other Fasinex products are relevant:

- 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.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

Data were presented for the previous extension application for Fasinex 100, 10% Oral Solution for Sheep. Direct entry of the active substance into the environment was considered unlikely and residues of triclabendazole reach the soil environment directly in the excreta of treated sheep.

Metabolism data indicated that the primary route of excretion was via the faeces. Faecal residue consisted of a number of metabolites including the parent compound. Only 16% of the administered dose was seen to be excreted as triclabendazole. No metabolite in excreta represented 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.

[1] PEC=Predicted environmental concentration

Acceptable data were previously presented for cattle, for Fasinex 10%.
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 Fasinex 100, 10% Oral Solution for Sheep and Cattle is considered acceptable.

III.B Residues documentation

For the extension application to add cattle no new data was required.

A variation was approved in October 2008 to decrease the withdrawal period for meat from 56 days to 35 days for sheep. The withdrawal period for cattle is 56 days.

Withdrawal Periods

Based on the data provided above, a withdrawal periods are as follows:-

- Cattle (meat and offal) – 56 days
- Sheep (meat and offal) – 35 days
- Do not administer to animals producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

There is no requirement to supply information in this section of the dossier as this is an extension application with reference to two previously authorised products.

Pharmacokinetics

There is no requirement to supply information in this section of the dossier as this is an extension application with reference to two previously authorised products.

Tolerance in the Target Species of Animals

There is no requirement to supply information in this section of the dossier, as this is an extension application with reference to two previously authorised products.

Resistance

There is no requirement to supply information in this section of the dossier, as this is an extension application with reference to two previously authorised products.

IV.B Clinical Studies

There is no requirement to supply information in this section of the dossier, as this is an extension application with reference to two previously authorised products.

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.

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