ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep

PuAR correct as of 05/07/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0428/001/MR
Name, strength and pharmaceutical form	Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep
Applicant	Elanco Europe Ltd Lilly House Priestley Road Basingstoke Hampshire RG24 9NL
Active substance(s)	Ivermectin, Triclabendazole
ATC Vetcode	QP54AA51
Target species	Sheep over 3 months of age
Indication for use	Treatment of mixed trematode (fluke) and nematode or arthropod infections due to gastrointestinal roundworms, lungworms, liver fluke and nasal bots. Gastrointestinal nematodes (adult and immature): *Haemonchus contortus, Teladorsagia (Ostertagia) circumcincta*, Trichostrongylus spp, Cooperia spp, Nematodirus spp including *N. battus, Strongyloides papillosus*, Oesophagostomum spp, and adult *Chabertia ovina.* Inhibited larval stages and benzimidazole resistant strains of *Haemonchus contortus* and *Teladorsagia (Ostertagia) circumcincta* are also controlled. Liver fluke (mature, immature and early immature stages down to less than 1 week of age): *Fasciola hepatica* Lungworms (adult and immature):

	Dictyocaulus filaria Nasal bots (all stages): *Oestrus ovis*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Fixed combination application in accordance with Article 13(b) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition	20 April 2012
Date product first authorised in the Reference Member State (MRP only)	20 November 2007
Concerned Member States for original procedure	France, Ireland, Italy, Spain

I. SCIENTIFIC OVERVIEW

Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep is an oral suspension containing triclabendazole 50 mg/ml and ivermectin 1 mg/ml for use in the treatment and control of gastrointestinal nematodes, liver fluke, lungworms and nasal bots in sheep. The product may also be used to treat bendimidazole resistant *Haemonchus contortus* and *Teladorsagia circumcinta*. The recommended dose rate is 1 ml per 5 kg bodyweight. The product was authorised Nationally in the United Kingdom in November 2007.

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.[1] 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 ivermectin 1 mg/ml and triclabendazole 50 mg/ml, and excipients methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), benzyl alcohol, microcrystalline cellulose and carmellose sodium, povidone K30, propylene glycol, disodium phosphate dodecahydrate and purified water. The choice of the formulation and presence of preservative are justified.

The product is presented in white high density polyethylene (HDPE) bottles of nominal capacity 0.8, 2.2, 5.0 litres, and a 12.0 litre HDPE container. Blue polypropylene screw caps with a flip-top are used as closures for the smaller pack sizes; a blue HDPE screw cap is used on the 12 litre pack.

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. The manufacture of a batch of the product has been described. In-process checks are conducted for completeness of dissolution of soluble substances, for absence of foaming that might selectively remove suspended materials from the bulk, and for

[1] SPC – Summary of Product Characteristics.

homogeneity, freedom from aggregates and viscosity increase in the final stages. Filled containers are check-weighed, with limits reflecting 100 - 103 % of the claimed content. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance ivermectin is an established active substance described in the European Pharmacopoeia (Ph. Eur.) A copy of the current EDQM certificate of suitability has been provided. No testing additional to that specified in the monograph of the European Pharmacopoeia is carried out.

Triclabendazole is described in the Ph. Eur. A copy of the current EDQM certificate of suitability has been provided.

Dispersible cellulose, an intimate mixture of microcrystalline cellulose and carmellose sodium, is the subject of a monograph in the British Pharmacopoeia. All other substances 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.

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

There are no intermediate products. The suspension is not stored or transported in bulk.

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. Tests include those for appearance, pH, density, and resuspendability.

G. Stability

The Certificate of Suitability for ivermectin specifies a 3 year retest interval for material stored in the commercial container, double-lined polyethylene bags within an aluminium drum.

The dossier includes a report on stability tests carried out on three batches of triclabendazole. These have been stored in containers representative of commercial packaging for 12 months under VICH accelerated conditions, 40°C/75%RH, and for 36 months under both long-term conditions, 25°C/60%RH, and refrigeration, 5°C. Samples were tested and on the basis of the evidence, the proposed retest interval of 5 years is justified. No special conditions of storage are required.

Stability data on three batches the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Tests include those for appearance, density, resuspendability, pH and microbial purity.

J. Other Information

The shelf life of the veterinary medicinal product as packaged for sale is 18 months. After first opening the immediate packaging, the shelf-life is 12 months. The product should be stored in the closed original container.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Both active substances, triclabendazole and ivermectin, are well known and well established substances that have been used in veterinary medicine for a number of years. This is a full stand alone fixed combination product for sheep which is an oral flukicide and broad spectrum antiparasitic drench.

Fasimec Duo S 0.1%/5% Oral Suspension for Sheep is a white to cream-coloured oral suspension containing 5% triclabendazole and 0.1% ivermectin. It is administered orally at a dose rate of 2 ml/10 kg bodyweight (bw) which is equivalent to 0.2 mg ivermectin and 10 mg triclabendazole per kg bw. The administration may be repeated depending on the epidemiological situation.

III.A Safety Testing

Pharmacological Studies

Pharmacology:

Triclabendazole:
Triclabendazole is a member of the sulphide benzimidazole group of anthelmintics. It is metabolised in host animals by a first pass process to a sulphoxide which is thought to have anthelmintic activity and is subsequently metabolised to a sulphone, which is thought to be anthelmintically active as well.

Ivermectin:
Ivermectin is an avermectin. It has a broad spectrum of activity against nematode and arthropod species in many domestic animals and is used in man for the treatment of *Onchocerca volvulus*.

Pharmacodynamics:

Triclabendazole:
The triclabendazole mode of action is not fully clear but is thought to interfere with intracellular transport mechanisms and inhibit protein synthesis. It is active against the liver fluke *Fasciola hepatica*.

Ivermectin:
Ivermectin is a member of the macrocyclic lactone class. These substances bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarisation of the nerve or muscle cell, resulting in paralysis and death of the parasite. Mammals do not have glutamate-gated chloride channels; the macrocyclic lactones have a low affinity for other mammalian ligand-gated channels and do not readily cross the blood-brain barrier.

Pharmacokinetics:

Ivermectin:
Ivermectin is readily absorbed and reaches peak plasma concentration within 1 day. Afterwards plasma concentrations decrease with a half life of 2 to 5 days.

Triclabendazole:
Triclabendazole is readily absorbed, oxidised to triclabendazole sulphoxide and to triclabendazole sulphone. Peak plasma concentrations are reached within 1.5 days. Afterwards plasma concentrations decrease with a half life of about 1 day. Both metabolites bind strongly to plasma proteins, particularly albumin. More than 90% of the dose is excreted in the faeces, about 2% in the urine and less than 1% in the milk within 10 days.

As the applicant described, the two actives are well characterised and have been used in veterinary medicine for a number of years. The mode of action of both actives is different and it is unlikely that there could be interference between

these two mechanisms. In order to investigate the likelihood of any interference in the absorption, distribution, metabolism and excretion, the applicant conducted a bioequivalence study comparing the profiles of the single actives to that of the combination. There is no indication from the pharmacokinetic studies of any interference between triclabendazole and ivermectin.

Toxicological Studies

Single dose toxicity:

Triclabendazole:
Studies indicated that triclabendazole is of low acute toxicity when administered by the oral, intraperitoneal, dermal and inhalation routes in rats and mice. 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.

Ivermectin:
Acute studies were conducted in mice, rats, rabbits, dogs and monkeys. The typical signs of acute ivermectin toxicity were all attributed to effects on the central nervous system. These were most severe in CF-1[2] mice. Approximately 30% of collie dogs were highly sensitive to ivermectin. In immature rhesus monkeys no tremors or convulsions occurred. The steep dose response curve in rodents was not reproduced in monkeys.

Acute oral toxicity
A test to determine the acute oral toxicity of the combination was conducted in rats. Rats were administered a single oral dose of 3000 mg/kg (Limit test) followed by a 14-day post treatment observation period. The study was conducted to GLP and there was no mortality or other treatment related abnormalities. Body weights and body weight changes were not affected by treatment and necropsy examinations did not reveal any treatment related effects. LD_{50} > 3000 mg/kg.

Acute dermal toxicity
A test to determine the acute dermal toxicity of the combination was conducted also in rats. These were administered a single dermal dose of 4000 mg/kg (Limit test) for 24 hours under semiocclusive conditions followed by a 14-day post treatment observation period. The study was conducted to GLP and there was no mortality or other treatment related abnormalities. Body weights and body weight changes were not affected by treatment except for one rat where a slight loss of body weight was recorded. Necropsy examinations did not reveal any treatment related effects. LD_{50} > 4000 mg/kg.

[2] A strain of mouse used in toxicological

Repeated dose toxicity:

Triclabendazole:
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 were seen 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[3] = 0.7 mg/kg bw). A 13-week feeding study in dogs (10, 100 or 1000 mg/kg feed triclabendazole) gave rise to a NOEL of 10 mg/kg feed (0.35 mg/kg bw).

Ivermectin:
Short-term studies were conducted in rats, dogs and monkeys. In a 14-week study in rats ivermectin was administered orally to pregnant dams, the NOEL was 0.4 mg/kg bw.

In a 14-week oral study in beagle dogs the NOEL was 0.5 mg/kg bw.

In a two-week oral study, ivermectin was administered to neonatal monkeys at 0.04 and 0.1 mg/kg bw and to immature monkeys at 0.3, 0.6 and 1.2 mg/kg bw. No treatment-related effects were observed. In a short-term escalating dose study in monkeys, an NOEL of 1 mg/kg was identified.

Tolerance in the target species:

Triclabendazole:
In sheep, single oral doses of 100 mg/kg and 125 mg/kg bw were tolerated with minor adverse effects.

Ivermectin:
Ivermectin is generally well tolerated in the intended target species, with occasional coughing in sheep after oral administration. Neurotoxic effects similar to those seen in laboratory species may occur in over dosage.

A study was performed on groups of sheep receiving one, five or ten times the recommended dose. No significant deviations from normal health state and normal values of measured parameters were detected in animals treated at one or five times the recommended dose. Increased liver weight and slightly increased clinical laboratory parameters were observed in the group that received 10 times the recommended dose. Therefore, it can be concluded that the product is well tolerated in sheep.

[3] NOEL = No Observed Effect Level

Reproductive toxicity (inc. teratogenicity):

Triclabendazole:
In a two-generation study in rats, animals were exposed to dietary levels of 3, 15 and 75 mg/kg feed triclabendazole. Neonatal survival and bodyweight were decreased at 15 and 75 mg/kg feed in the F2 generation but not in the F1 generation. A NOEL was determined at 3 mg/kg feed (0.15 mg/kg bw/day).

There was no evidence of teratogenicity in rats following oral administration with daily doses of 10, 30 or 100 mg triclabendazole/kg bw on gestation days 6-16. Foetal development was retarded at 100 mg/kg associated with maternal toxicity. In rats exposed to 10, 25, 50 or 100 mg/kg on gestation days 8-15, decreased maternal and foetal bodyweight gains were observed at 100 and 200 mg/kg. The overall NOEL for these studies was 50 mg/kg bw. Rabbits were exposed to doses of 3, 10 and 20 mg/kg on gestation days 6-18. Maternal toxicity and retarded foetal development was observed at 10 and 20 mg/kg. 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. 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.

Ivermectin:
In a three-generation study, neonatal toxicity was observed at 0.4 mg/kg bw with increased neonatal mortality up to about 10 days post-partum and decreased bodyweight in the survivors. A cross-fostering study indicated that the neonatal toxicity was not related to *in-utero* exposure but post natal exposure via maternal milk. There is evidence that neonatal rats are hypersusceptible to avermectin toxicity.

The developmental toxicity of ivermectin was investigated in mice, rats, rabbits and dogs. The results demonstrated that teratogenic effects were produced only at doses similar to those causing severe maternal toxicity. The NOEL for teratogenicity in the most sensitive species and strain, the CF-1 mouse was 0.2 mg/kg bw, while the NOEL for maternal toxicity was 0.1 mg/kg bw. The CF-1 mouse has a genetic predisposition to avermectin toxicity. No teratogenic or maternotoxic effects were observed in dogs given oral doses of 0.5 mg/kg bw every five or ten days from days 5 to 40 of gestation.

Mutagenicity:

Triclabendazole:
Triclabendazole was clearly negative in numerous *in-vitro* and *in-vivo* mutagenicity tests, including the Ames test.

Ivermectin:
Ivermectin was negative for mutagenic effects in a bacterial gene mutation study, a mouse lymphoma assay, and an Unscheduled DNA (deoxyribonucleic

acid) Synthesis (UDS) study in human fibroblasts (to 1000 µg/ml). The two components were negative in a bacterial gene mutation study.

Carcinogenicity:

Triclabendazole:
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 top dose group only (300 mg/kg in the diet).

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

A chronic toxicity/carcinogenicity study in rats (3, 13, 30 or 100 mg/kg in the diet for 2 years) demonstrated no statistically or biologically significant effects on survival, clinical findings, food or water intake, haematology, biochemistry, urinalysis or tumour incidences at any dose. Bodyweight gain was significantly depressed in the high dose females and kidney weights were lower in the high dose males at 52 weeks. The NOEL was 30 mg/kg feed (equivalent to about 1.5 mg/kg bw/day).

Ivermectin:
No carcinogenicity studies were performed. However, such data were not considered necessary on the basis of the absence of structural alerts and the results of the mutagenicity studies.

Other Studies

No specific studies were provided concerning potential immunotoxicity. The results of laboratory animal studies and clinical use in humans gave no indications of any effect on the immune system.

Observations in Humans

Triclabendazole:
Triclabendazole has 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 Fasciola 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.

Ivermectin:
Ivermectin is widely used in humans for treatment of onchocerciasis and other parasitic diseases at single or repeated doses of 0.15 to 800 mg/kg bw. Tolerance to the compound has been assessed in healthy volunteers and in patients; adverse effects are usually mild and transient. In particular, no effects on the central nervous system were observed. The main effects noted in field and community based trials have been those arising from the death of the parasites which is characterised by arthralgia, fever, hypertension, tachycardia, headache and ocular changes. Neither in these studies nor during treatment for other parasitic diseases has a subset of atypically sensitive individuals been detected. Also, the adverse effects experienced by the small number of persons accidentally exposed to doses (often of veterinary preparations) higher than customary human doses are in keeping with those noted in test animals.

A double blind, randomised, placebo controlled clinical trial was conducted to assess the safety and tolerability of oral subacute repeat doses of up to 1.2 mg/kg bw and an acute dose of 2.0 mg/kg bw in 68 healthy adult male and female human subjects as a treatment for headlice. No treatment related signs of toxicity were observed. A NOEL of 420 µg/kg bw was identified.

Microbiological Studies

Triclabendazole:
Triclabendazole has no significant antimicrobial activity.

Ivermectin:
No data on the effects of ivermectin of the human gut flora or micro-organisms used in food processing were available. However, such data were not considered necessary for this class of compound.

Studies on metabolites impurities, other substances and formulation:
In a study on acute eye irritation/corrosion in the rabbit 0.1 ml of the product was instilled into the conjuctival sac of the left eye of each animal while the right eye remained untreated and served as control. The eyes were examined for irritation at 1, 24, 48 and 72 hours after treatment. Hyperaemic conjuctival blood vessels were seen in all animals at the 1-hour reading only. All eye reactions were clear by day 1. There was no mortality and no other significant clinical or body weight changes. Therefore, it was concluded that it is not classified as irritant to the eye according to Commission Directive 93/21/EEC.

In a study on skin sensitisation, guinea pigs were split into two groups, a vehicle control group and a test group. There were no positive skin reactions among either the vehicle control or test group animals. There was no mortality and no other significant clinical or body weight changes. Therefore, it was concluded that it is not classified as skin sensitizer according to Commission Directive 93/21/EEC.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is safe for the user when used as recommended. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- People with known hypersensitivity to the active substances should avoid contact with the product. Protective gloves should be worn when handling the veterinary medicinal product.
- In case of accidental spillage onto skin or into the eyes wash immediately with water. Take off any contaminated clothes.
- Do not eat, drink or smoke whilst handling the product. Wash hands and exposed skin before meals and after work.

Ecotoxicity

The applicant provided an environmental risk assessment in compliance with the relevant guideline.

Animals are treated orally and residues of the active substances will enter the soil environment directly through excretion of urine and faeces.

Metabolism and excretion studies in sheep have shown that triclabendazole is excreted almost all in faeces. Parent compound is the major component of faecal residue (16% of the dose). The main route of excretion of ivermectin is also the faeces with 61-69% of the dose excreted in faeces as ivermectin. For both actives the greatest exposure is to dung fauna.

Information has been provided which demonstrates that there will not be any additional toxicity due the presence of two actives in the product. The risk assessment was carried out on each active individually on the basis that each was excreted only as parent compound.

Triclabendazole has been shown to be non-mobile in soil and slightly persistent. Ivermectin is also non-mobile in soil but is considered persistent in soil. Based on these properties leaching to groundwater and surface waters is negligible for both compounds. The PEC_{soil}[4] for ivermectin is very low <1 µg/kg and accumulation of residue is not considered to be a risk.

Information was provided that demonstrated that triclabendazole will not bioaccumulate. The PEC of ivermectin was calculated for soil, groundwater and surface water. Comparison of these PEC values with the results of effects studies in soil and aquatic organisms demonstrated that the risk to the soil and aquatic environments is acceptable.

[4] PEC_{soil} = Predicted Environmental Concentration of a substance in soil

Environmental safety of Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep is considered acceptable and the following warnings have been included on the SPC:

- Ivermectin is very toxic to aquatic organisms and dung insects.
- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. Dangerous to fish and other aquatic life. Do not contaminate ponds, waterways or ditches with the product or used container.

III.B Residues documentation

The applicant submitted a number of published references and in-house studies to address the issue of residues. Some of these studies were on the individual actives. The bioequivalence study was also submitted to show bioequivalence of the levels of the active substances when used alone and in combination. A residue depletion study using the product has also been submitted.

The residue depletion study using the final formulation was conducted in young sheep. Samples of muscle, kidney, fat and liver were taken from animals at several time points. Ivermectin levels were below the LOQ[5] from the first time point except in renal fat where detectable residues were reported. The determinant factor was triclabendazole residue levels

The analytical methods employed for the determination of both triclabendazole and ivermectin residues were also acceptable. The method was fully validated. Based on the maximum residues limited a withdrawal period of 27 days for meat in sheep is justified.

The product is not permitted for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Pharmacology

Pharmacodynamics

The applicant has presented references detailing the action of avermectins, including ivermectin, which potentiate or gate, the opening of glutamate-gated chloride channels, found only in invertebrates, resulting in paralysis and death. The references support the fact that triclabendazole has activity against early immature, immature and adult *Fasciola hepatica* and *Fasciola gigantica*, but no nematodicidal activity and that ivermectin has a broad spectrum of activity against a range of gastro-intestinal nematodes and of arthropods.

[5] LOQ=Limit of Quantification

Pharmacokinetics

Literature references have been provided by the applicant that demonstrate the expected pharmacokinetic profiles of ivermectin and triclabendazole. These are acceptable as stand alone supportive evidence, although the data they provide cannot be used to assess bioequivalence to the final formulation, as different formulations were used, than that of the proposed product.

The applicant was unable to show bioequivalence for ivermectin in any pharmacokinetic study, due to individual animal variations. However, this is not uncommon with ivermectin. The applicant later demonstrated bioequivalence of ivermectin, via pharmaceutical end points in clinical trials

The bioequivalence of triclabendazole was addressed in terms of its two active metabolites. However, the applicant was only able to show bioequivalence of one of the actives) inside the normal 80-125% range. The other metabolite) was shown to be equivalent if the wider limits of 70-143% were applied. These wider limits were fully justified by the applicant.

Tolerance in the Target Species

The applicant provided reference to a tolerance in the target species study. There was increased liver weight seen in all of the super-clinical dose rate groups. It is likely that this is of no clinical significance as there were no other significant changes in haematology, biochemistry, clinical examination, or pathology, and increased liver weight is a common occurrence after dosing with triclabendazole. This reference is supported by extensive PSUR[6], with an overall incidence on 0.00008% adverse reactions recorded. The applicant has provided no specific local tolerance data for this proposed product. The applicant has stated that there was only one PSUR report linked to oral problems, and this was thought to be related to incorrect dosing and subsequent pneumonia. There were no reported instances of local intolerance in any of the field trials. This is acceptable as supportive of local tolerance of the proposed product.

Resistance

The applicant has addressed the issue of resistance and adequate warnings and precautions appear on the SPC:

- 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 bodyweight, misadministration of the product or lack of calibration of the dosing device (if any).

[6] PSUR=Periodic Safety Update Report

- 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 ivermectin has been reported in *Teladorsagia (Ostertagia) circumcincta* in sheep and resistance to triclabendazole has been reported in *Fasciola* species in small ruminants in a number of countries including the EU. Therefore the use of this product should be based upon local (regional, farm) epidemiological information about susceptibility of the *Teladorsagia (Ostertagia) circumcincta* and recommendations on how to limit further selection for resistance to anthelmintics

Clinical Efficacy

Clinical trials provide evidence of the bioequivalence of the ivermectin component of the formulation as previously stated. The reference product used was equivalent to one authorised within the UK and consequently extrapolation of treatment claims may be made on this basis. The risk benefit assessment for Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep is favourable. References to trials also support the proposed treatment claims of the product.

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.

(www.gov.uk/check-animal-medicine-licensed)