IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

PRODUCT SUMMARY

Name, strength, pharmaceutical form	Tribamec Duo 50 mg/ml & 1mg/ml Oral Suspension for Sheep
Active substances	Triclabendazole, Ivermectin
Applicant	Chanelle Pharmaceuticals Manufacturing Limited
Legal basis of application	Generic application in accordance with Article 13.1 of Directive 2001/82/EC, as amended
Target species	Sheep
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*
ATCvet code	QP54AA51
Date of authorisation	20/01/2023

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released onto the market.
It has been shown that the product can be safely used in the target species sheep, any reactions observed are indicated in the SPC.
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. Qualitative and Quantitative Particulars

The product contains 50 mg/ml of triclabendazole and 1 mg/ml of ivermectin. The product contains the excipients: Microcrystalline cellulose and carmellose sodium, povidone K30, benzyl alcohol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, propylene glycol, polysorbate 20, simethicone emulsion, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate and purified water.
The product is filled into white high density polyethylene (HDPE) containers, in pack sizes of 1 L, 2.5 L, 3 L, 5 L and 10 L.
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 at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance triclabendazole is an established substance, described in the European Pharmacopoeia. The active substance ivermectin is an established substance, described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are considered adequate to control the quality of the respective materials. Batch analytical data demonstrating compliance with the respective specifications has been provided.
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on Intermediate Products

Not applicable.

E. 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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substances has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This marketing authorisation application was submitted in accordance with Article 13.1 (generic application) of Directive 2001/82/EC, as amended.
The product contains ivermectin and triclabendazole. The product is to be administered at a dose of 0.2 mg ivermectin/kg and 10 mg triclabendazole/kg by the oral route.
The applicant has conducted an *in vivo* bioequivalence study, comparing the bioavailability of ivermectin and triclabendazole in Tribamec Duo 50 mg/ml and 1 mg/ml Oral Suspension for Sheep with the reference product Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep (Elanco GmbH). The results of this study demonstrated that Tribamec Duo 50 mg/ml and 1 mg/ml Oral Suspension for Sheep is bioequivalent to the reference product in accordance with the relevant guidelines. As bioequivalence with a reference product (Fasimec Duo 50 mg/ml + 1 mg/ml Oral Suspension for Sheep) has been demonstrated, results of safety and residues tests and of pre-clinical and clinical trials are not required.
The safety and efficacy aspects of this product when used in sheep are identical to the reference product.

User Safety

Given that bioequivalence has been demonstrated with the reference product and that the exposure scenarios and the quantity of product to which the user may be exposed will be similar, any risk to user safety from the active substances will be the same as that for the reference product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, and will account for any differences in excipients.

Environmental Risk Assessment

Phase I

The calculated predicted environmental concentrations in soil (PEC_{soil}) for both ivermectin and triclabendazole for sheep were <100 µg/kg. However, as the Phase I assessment showed that ivermectin and triclabendazole are ectoparasiticides and endoparasiticides for use on pasture animals, a Phase II ERA is required.

Phase II

A Phase II Tier A and B assessment was conducted the results of which are summarised below.

Physico-chemical properties - Ivermectin	
Study type	**Result**
Vapour pressure	$<1.5 \times 10^{-9}$ mm Hg (2.0×10^{-7} Pa)
Water solubility	4 mg/L
n-Octanol/Water Partition Coefficient	$\log K_{ow}$ = 4.4 (estimated)

Environmental fate - Ivermectin	
Soil Adsorption/Desorption	K_{oc} = 12,660 ml/g K_d = 333 ml/g
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 20.5 days

Effect studies - Ivermectin			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Pseudokirchneriella subcapitata*	EC_{50}	4,000	µg/l
Daphnia spp. immobilisation	EC_{50}	0.0057	µg/l
Daphnia magna, reproduction (Tier B)	NOEC	0.0000003	µg/l
Fish, acute toxicity/*Salmo salar*	LC_{50}	1.7	µg/l
Earthworm/*Eisenia foetida*	EC_{50}	4.0	mg/kg
Sediment dwelling organism/*Chironomus riparius*	NOEC	6.3	µg/kg dry weight
Dung fly larvae/*Scathophaga stercoraria*	EC_{50}	20.9	µg/kg fresh weight
Dung beetle larvae/*Aphodius constans*	LC_{50}	392	µg/kg wet weight

Physico-chemical properties - Triclabendazole	
Study type	**Result**
Water solubility	0.02 mg/L
n-Octanol/Water Partition Coefficient	$\log K_{ow}$ = 6.0 (25°C, pH 5)

Environmental fate - Triclabendazole	
Soil Adsorption/Desorption	K_{oc} = 36,690.3 ml/g K_d = 448.0 ml/g
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 70.5 days

Effect studies - Triclabendazole			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Pseudokirchneriella subcapitata*	EC_{50}	13.5	µg/l
Daphnia spp. immobilisation	EC_{50}	141	µg/l
Fish, acute toxicity/*Oncorhynchus mykiss*	LC_{50}	75	µg/l
Earthworm/*Eisenia andrei* reproduction	NOEC	3.2	mg/kg dry weight
Dung fly larvae/*Scathophaga stercoraria* L.	NOEC	252	mg/kg wet weight
Dung beetle larvae/*Aphodius constans*	EC_{50}	656.7	µg/kg wet weight
Bioaccumulation in fish/*Oncorhynchus mykiss*	BMF BCF	0.0017 1233.3	kg/kg L/kg (estimated)

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.

Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.

In accordance with the guidance, the risk quotients for each of the active substances were summed. The risk characterisation resulted in risk quotients below 1 for the groundwater and soil compartments indicating that the product will not pose a risk to those compartments when used as recommended.

The results of the assessment for the surface water and dung compartments indicate that a risk for the environment potentially exists for aquatic invertebrates in surface waters and dung dwelling organisms. Consequently, the following warning is required for this product:

Ivermectin is very toxic to aquatic organisms and dung insects.

PBT Assessment

An assessment of ivermectin and triclabendazole in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether they may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.

The log K_{ow} of ivermectin was estimated to be 4.4. The log K_{ow} of triclabendazole was demonstrated to be 6.0.

Ivermectin and triclabendazole are not considered to be either PBT or vPvB.

Conclusion

Based on the data provided in the ERA, a risk to the aquatic and terrestrial environment cannot be excluded. Therefore, suitable advice was included in the SPC for this product.

III.B Residues documentation

No residue depletion studies were conducted in sheep because bioequivalence has been demonstrated with the reference product and the withdrawal periods of the reference product can be applied to Tribamec Duo 50 mg/ml and 1 mg/ml Oral Suspension for Sheep.

Withdrawal Periods

Based on the bioequivalence data provided, a withdrawal period of 27 days for meat and offal in sheep is justified. The information listed on the product literature is the same as that of the reference product and is adequate to ensure safety of the consumer:

Meat and offal: 27 days.

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

IV. CLINICAL ASSESSMENT

IV.A. Pre-Clinical Studies

As this is a generic application according to Article 13.1 of Directive 2001/82/EC, as amended, and bioequivalence with a reference product has been demonstrated, pre-clinical studies are not required.

Tolerance in the Target Species of Animals

Based on bioequivalence data presented, it is considered that the test product does not present any greater risk to the target species sheep than the reference product.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.B. Clinical Studies

As this is a generic application according to Article 13.1 of Directive 2001/82/EC, as amended, and bioequivalence with a reference product has been demonstrated, clinical studies are not required. The efficacy claims for this product are equivalent to those of the reference 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, thebenefit/risk profile for the target species is favourable and the quality andsafety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.

This section 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.