Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tribamec Duo 50 mg/ml & 1mg/ml Oral Suspension for Sheep

Date Created: January 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Tribamec Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep
Applicant	EU Pharmaceuticals Ltd 37 Geraldine Road London SW18 2NR
Active substances	Triclabendazole Ivermectin
ATC Vetcode	QP54AA51
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*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	September 2021

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Tribamec Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep, the reference product for which was Fasimec Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep, authorised in the UK via the national MA procedure, in November 2007.

The product is indicated for use in sheep, for the treatment of mixed trematode (fluke) and nematode or arthropod infections due to gastrointestinal roundworms, lungworms, liver fluke and nasal bots, as shown on page two above. Off-label use in dogs should be avoided as severe adverse reactions may occur. In common with other avermectins, certain breeds of dogs, such as collies are especially sensitive to ivermectin, and particular care should be taken to avoid accidental consumption of the product.

The dose rate for oral use is 0.2 mg ivermectin and 10 mg triclabendazole per kg bodyweight equivalent to 2 ml/10 kg bodyweight. Bodyweight should be assessed accurately before calculating the dose. The product is for oral administration using a suitably calibrated dosing gun. The container should be shaken thoroughly before use. Drenching equipment should be cleaned before and after use.

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, any reactions observed are indicated in the SPC.[1] 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 [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 50 mg/ml triclabendazole and 1 mg/ml ivermectin, and the excipients methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, benzyl alcohol, microcrystalline cellulose and carmellose sodium, povidone, propylene glycol, polysorbate 20, simethicone emulsion, sodium dihydrogen, phosphate monohydrate, disodium phosphate dihydrate and purified water.

The container/closure system consists of 1L, 2.5L, 3L & 5L containers and closures, white HDPE flexi containers with a polypropylene cap, and an aluminium foil seal. A 10 L container and closure consisting of a high-density polyethylene (HDPE) white container with a HDPE cap and an aluminium foil seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are justified.
The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a series of basic mixing and additions, followed by suitable quality assessment and packing.

II.C. Control of Starting Materials

The active substances are triclabendazole and ivermectin established active 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 material. Batch analytical data demonstrating compliance with these specifications have been provided. Appropriate Certificates of Suitability were provided.

Details of the excipients are described in relevant pharmacopoeia, and packaging conforms to specifications.

II.C.4. Substances of Biological Origin

Declarations have been provided that no materials of human or animal origin are used within the manufacture of the active substances or any of the excipients. However, in regard to the finished product packaging, a declaration was provided that the use of animal material that conforms to the TSE guideline.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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 have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, identification of active substances and key excipients, particle size and microbial count.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 1 year.
Do not store above 30ºC.
Store in the original container in order to protect from light.
Protect from frost.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the application, where a bioequivalence study in sheep confirmed parity with the reference product, no additional pharmacological or toxicological studies were required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- People with known hypersensitivity to active substances or parabens should avoid contact with the product.
- This product may cause skin and eye irritation.
- Avoid direct contact with the skin and eyes.
- Protective gloves should be worn when handling the 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 any exposed skin before meals and after work.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product is a parasiticide used in pasture animals and a Phase II ERA was required. (Question 16 VICH decision tree).

The initial predicted environmental concentration (PEC) in soil of the active substances was lower than 100 µg/kg, (Question 17 VICH decision tree), but as the product is a parasiticide, a Phase II ERA was required.

Phase II Tier A:

A Phase II tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physico-chemical properties, environmental fate and effects. Studies were carried out separately with reference to the active substances. This was deemed acceptable.

Ivermectin

Physico-chemical properties

Parameter	Value	Guideline
Octanol water partition coefficient (K_{OW})	25 119 (log K_{OW} 5.6) (pH 7.2, 20 °C)	OECD 123
Molecular weight	875 g/mol	-
Vapour pressure	<1.5 x 10^{-9} mm Hg (2.0 x 10^{-7} Pa)	-
Water solubility	4 mg/L	OECD 105

Data were presented with regard to the fate and behaviour of ivermectin in the environment, as excreted from sheep. These were acceptable on analysis.

In one reference, ivermectin has been shown to undergo rapid photodegradation as a thin, dry film on glass with an estimated half-life of 3 hours. In a further reference, near the surface of open water under clear skies, the half-life is 12 hours in summer and 39 hours in winter. Supporting data observing the degradation of ivermectin in various soils and temperatures were provided. Suitable data on adsorption and desorption of ivermectin were also provided. Data submitted according to OECD 306 were also acceptable.

A large amount of data on a variety of PEC (predicted environmental concentration) calculations were provided, in relation to all organisms that might be affected by ivermectin. For the terrestrial compartment, there was minimal effect on plants and micro-organisms. From relevant PEC calculations, PNEC (predicted no-effect concentration) calculations were created.

Risk Characterisation (Risk Quotient)
Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal as follows.

Ivermectin

Organism	PEC	PNEC	RQ
Terrestrial compartment			
Dung fly	Dung 930 µg/kg$_{dwt}$	0.209 µg/kg$_{dwt}$	**4 450**
Dung beetle		8.8 µg/kg$_{dwt}$	**94.9**
Earthworms	Soil 0.64 µg/kg$_{dwt}$	40 µg/kg$_{dwt}$	0.016
Aquatic compartment			
Fish	Surface water run-off drainage Step 1: 0.00020 µg/l	0.0017 µg/l	0.12
Daphnia		0.000012 µg/l	**16.7**
Algae		40 µg/l	<0.00001
Daphnia	Surface water run-off drainage Step 2 (FOCUS): 0.000072 µg/l	0.000012 µg/l	**6.0**
Sediment dwellers	Sediment run-off drainage Step 1: 0.127 µg/kg$_{dwt}$)	0.007615 µg/l	**16.7**
	Sediment run-off drainage Step 2 (FOCUS): 0.007551 µg/kg$_{wwt}$	0.007615 µg/l	0.99
Groundwater ecosystem	Groundwater Step 1 (CVMP Equation 36)	0.0000012 µg/l	**500**

Organism	PEC	PNEC	RQ
	0.0006 µg/l		
	Groundwater Step 2 (FOCUS PEARL) 0.000001 µg/l	0.0000012 µg/l	0.83

As some RQ values were >1, (bold text), further assessment of the environmental risk was required. Following further analysis, conclusions were drawn with regard to acceptable risk.

Triclabendazole

Physico-chemical properties

Parameter	Value	Guideline
Octanol water partition coefficient (log K_{OW})	6.0 (K_{OW} 1 101 314.5) (pH 5.0, 25˚C).	OECD 123
Molecular weight	359.66 g/mol	-
Melting point	175°C	-
Water solubility	0.02 mg/L	OECD 105

Data were presented with regard to the fate and behaviour of triclabendazole in the environment, as excreted from sheep, rats, dogs, goats and rabbits. These were acceptable on analysis. The omittance of data on vapour pressure for this active substance was accepted in light of suitable data being provided for $PEC_{groundwater}$.

A large amount of data were submitted in relation to degradation studies, (in accordance with OECD 307) and the adsorption and desorption of triclabendazole in soil, in accordance with accepted guidelines. Suitable PEC values were provided for relevant soils, and terrestrial and aquatic compartments. From these and against relevant guidelines, appropriate PNEC values were derived.

Risk Characterisation (Risk Quotient)
Using the assessment factors (AF) in VICH guidelines PNEC concentrations were calculated and compared with the PEC values for each target animal as follows.

Triclabendazole

Organism	PEC	PNEC	RQ
Terrestrial compartment			
Dung fly	Dung 400 µg/kg_{wwt}	2.48 µg/kg_{wwt}	**161.3**
Dung beetle	Dung	6.567 µg/kg_{wwt}	**60 911**

Organism	PEC	PNEC	RQ
	400 µg/kg_{wwt}		
Earthworms	Soil 33.0 µg/kg_{dwt}	320 µg/kg_{dwt}	0.1
Aquatic compartment			
Fish	Surface water run-off drainage Step 1: 0.0037 µg/l	0.075 µg/l	0.049
Daphnia		0.141 µg/l	0.026
Algae		0.135 µg/l	0.027
Groundwater ecosystem	Groundwater Step 1 (CVMP Equation 36) 0.011 µg/l	0.0075 µg/l	**1.47**
	Groundwater Step 2 (FOCUS PEARL) 0.000001 µg/l	0.0075 µg/l	0.00013

As some RQ values were >1, (bold text), further assessment of the environmental risk was required. Following further analysis, conclusions were drawn with regard to acceptable risk.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because bioequivalence was claimed and confirmed with the reference product.

MRLs

As the product is intended for use in food producing species, the MRL status of the active substance and each excipient were clarified in accordance with Regulation (EC) No 470/2009. The applicant has confirmed that the active substances and the excipient, benzyl alcohol are included in Table 1 of the annex Regulation 37/2010. The remaining excipients are either included in Table 1 of the annex Regulation 37/2010 (MRLs established) or been shown to have no pharmacological activity at the dose administered (in line with EMA/CVMP/516817/2009) and entered on the official 'out of scope' list (EMA/CVMP/519714/2009 –Rev.44, 18 June 2020).

MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Triclabendazole	Sum of the extractable residues that may be oxidised to ketotriclabendazole	All ruminants	250 225 150 100 10	Liver* Muscle* Kidney* Fat* Milk	
Ivermectin	22,23-Dihydroavermectin B1a	All mammalian food producing species	100 100 30	Fat Liver Kidney	Not for use in animals producing milk for human consumption.

Withdrawal Periods

Based on the data provided, withdrawal periods were established as follows:
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 DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, no pharmacodynamic data were required. The applicant has conducted an *in vivo* bioequivalence study in sheep, in order to compare the pharmacokinetics of both active substances within the proposed and reference products. This study was a single dose, two group, parallel study. The parameters of the study followed the standard formula for such tests, with analysis taking place after a variety of days, followed by suitable statistical analysis. For AUC_{0-t} the 90% confidence intervals for relevant parameters fell within the limits of 80 - 125%.

For C_{max} the 90% confidence intervals for the relevant parameters fell within the widened limits of 70 - 143%, as pre-set and justified in the Study Plan.

Bioequivalence was suitably justified.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the application.

Resistance

Resistance studies were not required due to the nature of the application.

IV.II. Clinical Documentation

Clinical documentation was not required due to the nature of the application.

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 of the product is favourable.

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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