



**Veterinary
Medicines
Directorate**

**United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

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

Date Created: April 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Triclacert Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep, Oral paste
Applicant	EU Pharmaceuticals Ltd, 37 Geraldine Road, London, SW18 2NR
Active substance	Ivermectin Triclabendazole
ATC Vetcode	QP54AA51
Target species	Sheep
Indication for use	<p>Treatment of mixed trematode (flake) and nematode or arthropod infections due to gastrointestinal roundworms, lungworms, liver fluke and nasal bots:</p> <ul style="list-style-type: none"> Gastrointestinal nematodes (adult and immature): <ul style="list-style-type: none"> <i>Haemonchus contortus</i>, <i>Teladorsagia (Ostertagia) circumcincta</i>, <i>Trichostrongylus</i> spp, <i>Cooperia</i> spp, <i>Nematodirus</i> spp including <i>N. battus</i>, <i>Strongyloides papillosus</i>, <i>Oesophagostomum</i> spp, and adult <i>Chabertia ovina</i>. Inhibited larval stages and benzimidazole resistant strains of <i>Haemonchus contortus</i> and <i>Teladorsagia (Ostertagia) circumcincta</i> are also controlled. Liver fluke (mature, immature and early immature stages down to less than 1 week of age): <ul style="list-style-type: none"> <i>Fasciola hepatica</i> Lungworms (adult and immature): <ul style="list-style-type: none"> <i>Dictyocaulus filaria</i> Nasal bots (all stages): <ul style="list-style-type: none"> <i>Oestrus ovis</i>

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 8 of VMRs 2013 (Schedule 1, Para 10) as amended.
Date of conclusion of the procedure	15/04/2025

I. SCIENTIFIC OVERVIEW

This is a generic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10) as amended, for authorisations in Great Britain (GB) and Northern Ireland (NI). The reference product in GB and NI is Fasimec Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep. The reference product was authorised via the national MA procedure on 20 November 2007 in the UK, but the marketing authorisation has now expired in NI. The applicant provided evidence of bioequivalence with the reference product.

Triclacert Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep contains 50 mg of triclabendazole and 1 mg/ml ivermectin per ml of product. The indication is for the treatment of mixed trematode (flake) and nematode or arthropod infections in sheep, due to specified species of gastrointestinal roundworms, lungworms, liver fluke and nasal bots.

The dose is 0.2 mg ivermectin and 10 mg triclabendazole per kg bodyweight equivalent to 2 ml/10 kg bodyweight, administered orally using a dosing gun.

The distribution category for the product in NI and GB is POM-VPS, a veterinary medicinal product that may be prescribed by any Registered Qualified Person.

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 SPC¹. 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 efficacy² 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 triclabendazole and ivermectin and the excipients methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, benzyl alcohol, povidone, microcrystalline cellulose & carmellose sodium, propylene glycol, polysorbate 20, simethicone emulsion, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate and purified water.

The container/closure system consists of white HDPE flexi containers with a polypropylene cap and an aluminium foil seal for the 1 L, 2.5 L, 3 L & 5 L sizes, and a high-density polyethylene (HDPE), white container with a HDPE cap and an aluminium foil seal for the 10 L size. 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 regulatory 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 is a standard process consisting of two phases, which are then mixed, and the final excipients are added.

Process validation data on the product have been presented in accordance with the relevant regulatory guidelines.

II.C. Control of Starting Materials

The active substances are triclabendazole and ivermectin, both established active substances supplied with valid certificates of suitability. 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 excipients used in the product are tested in line with the relevant monograph.

The packaging materials meet the relevant food contact guidelines and comply with the appropriate regulations.

II.C.4. Substances of Biological Origin

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

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 site have been provided demonstrating compliance with the specification. Control tests on the finished product are those appropriate for the pharmaceutical form.

II.F. Stability

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

G. Other Information

The shelf life of the veterinary medicinal product as packaged for sale is 18 months. The shelf life after first opening the immediate packaging is 1 year. The product should be stored in the original container and protected from light. The product should not be stored above 30 °C, should not be frozen and should be protected from frost.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACOTOXICOLOGICAL)

Due to the legal basis of the applications, no new pharmacological or toxicological studies were submitted. Appropriate bioequivalence data to the reference product was provided.

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/consumers.

III.A Safety Documentation

Pharmacological Studies

Bibliographical data was provided which show the pharmacodynamics of the active substances.

Ivermectin is an avermectin which interact with glutamate-gated chloride ion channels, to increase membrane permeability to chloride ions, causing irreversible neuromuscular blockade in nematodes and arthropods, followed by paralysis and death.

Triclabendazole interferes with intracellular transport mechanisms and inhibits protein synthesis and is active against the liver fluke *Fasciola*.

The applicant also provided bibliographical data which show the pharmacokinetic properties of the active substances.

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

Triclabendazole is readily absorbed, oxidised to triclabendazole sulfoxide and to triclabendazole sulfone. Peak plasma concentrations are reached within 2 days. Afterwards plasma concentrations decrease with a half-life of about 1.5 days. 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.

The inter-individual variability of the kinetics of ivermectin and metabolites of triclabendazole in ovine species is high.

The applicant submitted an *in-vivo* blood bioequivalence study in sheep, comparing the pharmacokinetics of the candidate product to the reference product, Fasimec Duo 50 mg/ml & 1 mg/ml Oral Suspension for Sheep. The study was designed using a randomised, single dose, two group, parallel study design which was justified. The results demonstrated acceptable bioequivalence between the products.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the product does not present an unacceptable risk to the user if used as directed.

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:

- This product may cause hypersensitivity (allergic) reactions. People with known hypersensitivity to ivermectin, triclabendazole 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})	$\log K_{OW}$ 5.6 (pH 7.2, 20 °C)	OECD 123
Molecular weight	875 g/mol	-
Vapour pressure	$<1.5 \times 10^{-9}$ mm Hg (2.0×10^{-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	0.209 µg/kg _{dwt}	17 110
Dung beetle	3576 µg/kg _{dwt}	8.8 µg/kg _{wwt}	406
Earthworms	Soil 0.64 µg/kg _{dwt}	40 µg/kg _{dwt}	0.016
Aquatic compartment			
Fish	Surface water	0.003 µg/l	0.07
<i>Daphnia</i>	run-off drainage	0.0000057 µg/l	16.7
Algae	Step 1: 0.00020 µg/l	40 µg/l	<0.00001
<i>Daphnia</i>	Surface water run-off drainage Step 2 (FOCUS): 0.000069 µg/l	0.000012 µg/l	5.8
Sediment dwellers	Sediment run-off drainage Step 1: 0.127 µg/kg _{dwt})	0.00362 µg/kg _{dwt}	35.1
	Sediment run-off drainage Step 2 (FOCUS): 0.007026 µg/kg _{wwt}	0.00362 µg/kg _{dwt}	1.94
Groundwater ecosystem	Groundwater Step 1 (CVMP Equation 36) 0.0006 µg/l	0.0000012 µg/l	500

Organism	PEC	PNEC	RQ
	Groundwater Step 2 (FOCUS PEARL) 0.00000049 µg/l	0.00000057 µg/l	0.86

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 omission 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 400 µg/kg _{wwt}	6.567 µg/kg _{wwt}	60 911
Earthworms	Soil 33.0 µg/kg _{dwt}	320 µg/kg _{dwt}	0.1

Organism	PEC	PNEC	RQ
Aquatic compartment			
Fish	Surface water run-off drainage Step 1: 0.0038 µg/l	0.075 µg/l	0.051
<i>Daphnia</i>		0.141 µg/l	0.027
Algae		0.135 µg/l	0.028
Groundwater ecosystem	Groundwater Step 1 (CVMP Equation 36) 0.0113 µg/l	0.0075 µg/l	1.51
	Groundwater Step 2 (FOCUS PEARL) 0.000001 µg/l	0.0075 µg/l	0.00007

As some RQ values were >1, (**bold text**), further assessment of the environmental risk was required. Following further analysis, conclusions were drawn regarding acceptable risk. Risk mitigation measures and environmental warnings regarding the risks identified for dung fauna and the aquatic compartment, which were comparable to similar recently authorised products, were agreed.

III.B.2 Residues documentation

Residue Studies

Due to the legal basis of this application, no studies were required to be provided in relation to residues.

MRLs

Triclabendazole is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues/milk. The marker substance is the sum of the extractable residues that may oxidised to keotriclabendazole.

MRLs are listed below:

	All ruminants
Muscle	225 µg/kg
Liver	250 µg/kg
Kidney	150 µg/kg
Fat	100 µg/kg
Milk	10 µg/kg

Ivermectin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues. The marker substance is 22, 23-Dihydroavermectin B 1a.

MRLs are listed below:

	All mammalian producing species
Muscle	30 µg/kg
Liver	100 µg/kg
Kidney	30 µg/kg
Fat	100 µg/kg

Withdrawal Periods

Based on the data provided, a withdrawal period of 27 days for meat and offal is justified the product is not permitted for use in ewes producing milk for human consumption, including during the dry period. It is specified not to use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

IV. CLINICAL DOCUMENTATION

As these are generic applications, and bioequivalence with the reference product has been established, efficacy studies are not required. The efficacy claims, dosing regimens, and pharmacology for this product are equivalent to those of the reference product.

Resistance

The bibliography/information provided demonstrates the level of ivermectin and triclabendazole resistance in the GB sheep population. Resistance to ivermectin has been reported in *Teladorsagia (Ostertagia) circumcincta*, *Haemonchus contortus* and *Trichostrongylus* species in sheep, and increasing resistance to triclabendazole has been reported in *Fasciola* species in sheep in several countries including in Europe.

Adequate warnings and precautions appear on the product literature.

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.

[\(www.gov.uk/check-animal-medicine-licensed\)](http://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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