



**Veterinary
Medicines
Directorate**

**United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

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

Tramazole 100 mg/ml Oral Suspension for Cattle and Sheep

Date Created: May 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Tramazole 100 mg/ml Oral Suspension for Cattle and Sheep
Applicant	Tulivin Laboratories Ltd 35 Abbeydale Park Newtonards Co. Down Northern Ireland BT23 8RE
Active substance	albendazole
ATC Vetcode	QP52AC11
Target species	Cattle and sheep
Indication for use	<p>A broad spectrum multi-purpose anthelmintic for the control of mature and developing immature forms of gastrointestinal roundworms, lungworms, tapeworms and adult liver fluke in cattle and sheep. The product is also ovicidal against fluke and roundworm eggs, thus reducing pasture contamination.</p> <p>In cattle the product is active against the following species: Roundworms: <i>Ostertagia</i>, <i>Haemonchus</i>, <i>Trichostrongylus</i>, <i>Nematodirus</i>, <i>Oesophagostomum</i>, <i>Bunostomum</i>, <i>Cooperia</i> and <i>Strongyloides</i> spp. It is usually effective against inhibited larvae of <i>Cooperia</i> and <i>Ostertagia</i>, Lungworms: <i>Dictyocaulus viviparus</i>, Tapeworms: <i>Moniezia</i> spp., Adult liver fluke: <i>Fasciola hepatica</i></p> <p>In sheep, the product is active against benzimidazole-susceptible strains of the following species: Roundworms: <i>Ostertagia</i>, <i>Haemonchus</i>,</p>

	<p><i>Trichostrongylus</i>, <i>Nematodirus</i>, (including <i>N.battus</i>), <i>Chabertia</i> and <i>Oesophagostomum</i>. It is usually effective against inhibited larvae of <i>Ostertagia</i>. Lungworms: <i>Dictyocaulus filaria</i>, Tapeworms: <i>Moniezia spp.</i>, Adult liver fluke: <i>Fasciola hepatica</i></p>
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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 12 (3) of Directive 2001/82/EC as amended.
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I. SCIENTIFIC OVERVIEW

This application was for an extension to the existing marketing authorisation of Tramazole 2.5% w/v SC Oral Suspension (Vm 11810/4007), which has been authorised in the UK since 1996. The lower strength product was authorised as an informed consent application of Albex 2.5% w/v SC Oral Suspension (Vm 11990/4015), authorised in the UK since 1996. Tramazole 2.5% contains 25 mg/ml albendazole. The current application is made in accordance with Article 12 (3) of Directive 2001/82/EC as amended.

The product is for use in cattle and sheep. In cattle, the product is for the treatment of the following roundworms: *Ostertagia*, *Haemonchus*, *Trichostrongylus*, *Nematodirus*, *Oesophagostomum*, *Bunostomum*, *Cooperia* and *Strongyloides* spp. It is usually effective against inhibited larvae of *Cooperia* and *Ostertagia*. The product may also be used for the treatment of lungworms: *Dictyocaulus viviparus*, tapeworms: *Moniezia* spp., and adult liver fluke: *Fasciola hepatica*. In sheep, the product may be used to treat roundworms: *Ostertagia*, *Haemonchus*, *Trichostrongylus*, *Nematodirus*, (including *N. battus*), *Chabertia* and *Oesophagostomum*. It is usually effective against inhibited larvae of *Ostertagia*. The product may also be used for the treatment of lungworms: *Dictyocaulus filaria*, Tapeworms: *Moniezia* spp., and adult liver fluke: *Fasciola hepatica*.

For cattle, the following dosages apply: for the control of roundworms, lungworms, tapeworms and fluke and roundworm eggs, dosage: 7.5 mg albendazole per kg bodyweight. (7.5 ml Tramazole 10% S&C per 100 kg bodyweight). Fluke and worm dose: For the additional treatment of adult liver fluke (chronic fascioliasis) in cattle, the dosage is 10 mg albendazole per kg bodyweight. (10 ml Tramazole 10% S&C per 100 kg bodyweight).

For sheep, the following dosages apply: for the control of roundworms, lungworms, tapeworms and fluke and roundworm eggs, dosage: 5 mg albendazole per kg bodyweight. (1 ml Tramazole 10% S&C per 20 kg bodyweight). Fluke and Worm Dose: For the additional treatment of adult liver fluke (chronic fascioliasis) in sheep, the dosage is 7.5 mg albendazole per kg bodyweight. (1.5 ml Tramazole 10% S&C per 20 kg bodyweight).

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, 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 100 mg/ml albendazole and the excipients methyl parahydroxybenzoate, propyl parahydroxybenzoate, green S E142, sodium selenite pentahydrate, cobalt sulphate heptahydrate, citric acid monohydrate, sodium citrate, xanthan gum, povidone 90, polysorbate 20, propylene glycol, simethicone emulsion and purified Water.

The container/closure system consists of 1 litre, 2.5 litre or 5 litre white, high density polyethylene rigid containers closed with a polypropylene screw cap, lined with a wood pulp liner coated with a polyvinylidene chloride film. 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The method of manufacture consists of the creation of an initial gel mixture, followed by addition of the remaining components during a series of mixing steps.

II.C. Control of Starting Materials

The active substance is albendazole, an established active substance described in the European Pharmacopoeia, and controlled by an acceptable Certificate 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.

¹ SPC – Summary of product Characteristics.

² Efficacy – The production of a desired or intended result.

Excipients described in a pharmacopoeia are sodium selenite pentahydrate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, citric acid monohydrate, sodium citrate, xanthan gum, povidone K90, polysorbate 20, propylene glycol and purified water, all described within the Ph. Eur. Simethicone emulsion complies with the United States Formulary monograph. Green S E142 and cobalt sulphate heptahydrate, (Ph. Eur cited), are supplied to the manufacturer's specifications.

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. Tests include those for appearance, identification assays, pH, related substances, fill uniformity, and microbial analysis.

II.F. 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. A re-test period of 5 years as stored in the approved packaging was approved. Data on three commercial-scale batches of the active substance showed that the product remained within agreed specifications.

Suitable data in line with VICH³ guidelines for demonstrating stability were provided on the finished product. Supporting data on the lower strength product were also provided. As no photostability studies were conducted, the statement 'protect from light' appears on the product literature and SPC.

H. Genetically Modified Organisms

Not applicable.

³ VICH - International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

J. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
- This veterinary medicinal product does not require any special storage conditions.
- Protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACOTOXICOLOGICAL)

Exemption was correctly claimed with regard to providing toxicological and pharmacological data for this application. The following criteria having been fulfilled in order to demonstrate that the two strengths of the product are pharmaceutically equivalent:

1. The two strengths of pharmaceutical product are manufactured by the same manufacturing process.
2. The qualitative composition of both strengths is the same (with the exception of the colouring agent included to differentiate between strengths).
3. Only the amount of active substance (and trace elements, cobalt and selenium) differs between the two strengths; the amount of each of the other excipients is the same.
4. The dose to be administered (and administration route) is the same for both strengths.
5. The indications and recommendations of use are the same for the different strengths.

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.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The risks from the product are the same as those of the lower strength product, albeit that the more concentrated product poses a four-fold greater exposure. The warnings cited on the SPC and product literature are the same as those of the reference product, this is acceptable. The data were updated sufficiently to include any changes to the relevant guideline since the authorisation of the reference product:

- This product can cause skin and eye irritation.
- Personal protective equipment consisting of suitable protective clothing, including impermeable rubber gloves, should be worn when handling the product.
- In case of accidental spillage onto skin, wash the affected area with soap and water. If irritation persists seek medical advice immediately and show the package leaflet or the label to the physician.
- In case of accidental eye exposure, flush eye thoroughly with running water. If irritation persists seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

Suitable data, based on that originally provided for the reference product were provided and accepted. The product literature and SPC carry suitable warnings:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
- Do not contaminate ponds, waterways or ditches with the product or used containers.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because bioequivalence with the reference product was established.

MRLs

Albendazole is listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 of December 22, 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

MRLs for albendazole are listed below for all ruminants. The marker residue was a combination of albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone expressed as albendazole:

	MRLs ($\mu\text{g}/\text{kg}$)	Target tissue
Muscle	100	Muscle
Liver	100	Fat
Kidney	1000	Liver
Fat / skin	500	Kidney
Milk	100	Milk

Withdrawal Periods

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

Cattle

Meat and offal: 14 days

Milk: 60 hours

Sheep

Meat and offal: 4 days

Do not use in sheep producing milk for human consumption

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

No *in vivo* bioequivalence studies were required because the proposed product was accepted as being bioequivalent to the reference product.

Tolerance in the Target Species

No tolerance studies were required because the proposed product was accepted as being bioequivalent to the reference product.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

No clinical studies were required because the proposed product was accepted as being bioequivalent to 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, the benefit/risk profile of the product(s) is favourable.

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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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