

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Combizole Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active Substances:

Levamisole Hydrochloride	37.5	mg
Fenbendazole	25.0	mg

Excipients

Formaldehyde Solution	2.0	mg
Potassium Sorbate	1.8	mg

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.

An aqueous milky white free flowing suspension.

4 CLINICAL PARTICULARS

4.1 Target Species

Sheep.

4.2 Indications for use, specifying the target species

For the treatment of roundworm, lungworm and tapeworm infections of sheep caused by:

Gastrointestinal Roundworms: *Bunostomum*, *Chabertia*, *Cooperia*, *Haemonchus*, *Nematodirus*, *Oesophagostomum*, *Ostertagia*, *Trichostrongylus*

Lungworms: *Dictyocaulus*

Tapeworm: *Moniezia* spp

The product is active against mature and immature parasite stages sensitive to fenbendazole or levamisole. Fenbendazole is ovicidal and will kill worm eggs.

4.3 Contraindications

Do not use in animals that are severely stressed or in ill-health.

4.4 Special warnings for each target species

Do not administer to sheep under stress or in poor condition.

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.

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 tests strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used.

4.5 Special precautions for use

Special precautions for use in animals

Do not exceed dose rates.

Care must be taken to avoid injury to the throat when drenching animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Direct contact with skin should be kept to a minimum.

Wear suitable protective clothing including impermeable rubber gloves.

Wash hands after use.

Levamisole can cause idiosyncratic reactions and serious blood disorders in a very small number of people. If symptoms such as dizziness, nausea, vomiting or abdominal discomfort are experienced when using the product, or sore mouth and fever occur shortly afterwards, seek medical advice immediately and show the package insert or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

Do not use in sheep producing milk for human consumption.

4.8 Interaction with other medicinal products and other forms of interactions

None known.

4.9 Amounts to be administered and administration route

Shake well before use.

To ensure administration of a correct dose, body weight should be determined as accurately as possible. If animals are to be treated collectively rather than individually they should be grouped according to their bodyweight and dosed accordingly, in order to avoid under- or over- dosing. Use properly calibrated dosing equipment.

Sheep: 1 ml per 5 kg bodyweight given orally delivers a dose of 7.5 mg/kg levamisole hydrochloride and 5 mg/kg fenbendazole.

For example:

BodyweightDose

Up to 10 kg	2 ml
10-15 kg	3 ml
16-20 kg	4 ml
21-25 kg	5 ml
26-30 kg	6 ml
Above 31 kg	add 1 ml per each 5 kg

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Symptoms of levamisole overdosing are similar to those of poisoning by organophosphorus compounds: salivation, constriction of the pupils and respiratory distress. Anaphylactic reactions have been reported. Treatment in these cases is with antihistamines. Extremely high dose of fenbendazole (up to 100 x therapeutic dose) would be required to cause any signs of depression and anorexia in sheep.

4.11 Withdrawal period(s)

Meat and Offal: 21 days

Not permitted for use in sheep producing milk for human consumption.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group:

Fenbendazole – Benzimidazole

Levamisole hydrochloride – Imidazothiazole

ATCvet Code:

QP52A

5.1 Pharmacodynamic properties

The primary mode of action is the prevention of microtubule polymerisation with consequent loss of the parasites' essential enzyme activities. Differential binding affinities between nematode and mammalian tubulin may explain the selective toxicity of Fenbendazole and other Benzimidazoles.

Levamisole stimulates both parasympathetic and sympathetic ganglia in parasitic worms, causing a rapid, reversible paralysis which allows them to be expelled from the gut by normal peristaltic action. High concentrations inhibit the fumerate reductase system, and this effect may contribute to anthelmintic action or be linked to the paralysing effects.

5.2 Pharmacokinetic particulars

Fenbendazole is slowly absorbed from the gastrointestinal tract and mostly excreted unchanged in faeces. In sheep, peak Fenbendazole blood levels occur and decrease slowly (t_{max} ~ 8 to 36 hours); C_{max} ~ 53 to 111 micrograms/L; $t_{1/2}$ ~ 2 to 3 days. The main metabolites in blood plasma are fenbendazole, oxfendazole and fenbendazole sulphone. Target tissue for residues is liver.

Levamisole is rapidly absorbed from the gastrointestinal tract. The percentage of the dose absorbed by the oral route ~ 50%. In sheep, peak levamisole blood levels occur and decrease rapidly (t_{max} ~ 1 to 2 hours); C_{max} ~ 350 to 1000 micrograms/L; $t_{1/2}$ ~ 3 hours. Residues of the drug are higher and more persistent in liver than in kidney or muscle tissue.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Citric Acid
Colloidal Anhydrous Silica
Formaldehyde Solution
Propylene Glycol
Polyoxyl Stearate
Potassium Sorbate
Polyethylene Glycol 6000
Xanthan Gum
Purified Water

6.2 Major incompatibilities

None known.

6.3 Shelf-life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container tightly closed.
Protect from light and frost.

6.5 Nature and composition of immediate packaging

White, food grade, high density polyethylene pack.
Closure: White, HDPE cap (screw fit)
Pack Size: 1 and 10 L Jerry can
2.5 and 5 L Back Pack
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Unused product or waste material should be disposed of in accordance with current practice for pharmaceutical waste under national waste disposal regulations.

Do not contaminate surface waters or ditches with the product or used containers as this may be dangerous for fish and other aquatic organisms.

7 MARKETING AUTHORISATION HOLDER

Bimeda Animal Health Limited
2, 3 & 4 Airton Close
Airton Road
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

VPA22033/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 February 2005
Date of last renewal: 03 February 2010

10 DATE OF REVISION OF THE TEXT

May 2019