

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Closivet 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance

Ivermectin	5	mg
Closantel (as Closantel Sodium Dihydrate)	200	mg

Excipients

Brilliant Blue FCF (E133)	0.1	mg
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For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pour-On solution.

A clear blue/green solution.

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle.

4.2 Indications for use, specifying the target species

For the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice of cattle.

Gastrointestinal roundworms (adults and fourth stage larvae)

Ostertagia ostertagi (including inhibited *O. ostertagi*), *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia* spp, *Oesophagostomum radiatum*, *Nematodirus helvetianus* (adult), *Strongyloides papillosus* (adult).

Lungworms (adult and fourth stage larvae)

Dictyocaulus viviparus

Trematodes (adult and late immatures)

Fasciola gigantica

Fasciola hepatica

Treatment of fluke at 12 weeks (mature) >95% efficacy.

Treatment of fluke at 7 weeks (late immature) >95% efficacy.

Eyeworms (adult)

Thelazia spp

Cattle grubs (parasitic stages)

Hypoderma bovis, *Hypoderma lineatum*

Lice

Linognathus vituli, *Haematopinus eurysternus*, *Damalinia bovis*

Mange Mites*Chorioptes bovis*, *Sarcoptes scabiei* var *bovis***4.3 Contraindications**

Do not use in cases of known hypersensitivity to the active substances.

Do not apply to areas of skin which have mange, scabs or other lesions or to areas contaminated with mud or manure.

Avermectins may not be well tolerated in non-target species (cases of intolerance with fatal outcome are reported in dogs – especially Collies, Old English Sheepdogs and related breeds or crosses, and also in turtles/tortoises).

4.4 Special warnings for each target species

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.

The effect of rain on the pour-on formulation at the time of and after application has not been investigated. For maximum effect animals should be kept indoors or undercover following treatment, when there is rain or an imminent risk of rain.

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.

Resistance to ivermectin has been reported in *Cooperia* spp in cattle. Therefore the use of this product should be based on local epidemiological information about the susceptibility of the *Cooperia* spp and recommendations on how to limit further selection for resistance to anthelmintics.

4.5 Special precautions for use**(i) Special precautions for use in animals:**

Due to the significant likelihood of cross-contamination of non-treated animals with this product due to grooming (licking), all animals in a group should be treated at the same time and treated animals should be kept separately from non-treated animals throughout the withdrawal period. Non-compliance with this recommendation may lead to residues violations (see section 4.11) or in very rare cases, it can lead to adverse events (see section 4.6) in non-treated animals.

Care should be taken to ensure animals are not overdosed by the application volume, accidental spillage or oral ingestion, as overdosage may result in signs of toxicity such as inco-ordination and blindness. It is recommended that animals are not clipped prior to treatment to reduce the risk of increased drug absorption and hence bioavailability, or oral ingestion through mutual grooming.

Care should be taken when treating animals which may be of low nutritional status as this may increase susceptibility of adverse events occurring.

(ii) Special precautions to be taken by the person administering the veterinary medicinal product to animals:

The veterinary medicinal product may be irritating to human skin and eyes and the user should be careful not to apply it to himself or other persons. Operators should wear nitrile rubber gloves and boots with a waterproof coat when applying the product. Protective clothing should be washed after use. If accidental skin contact occurs, wash the affected area immediately with soap and water. If accidental eye exposure occurs, flush the eyes immediately with water and get medical attention.

Do not smoke or eat whilst handling the product. Wash hands after use. Use only in well ventilated areas or outdoors.

(iii) Other Precautions Regarding the Environment.

Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases (less than 1 animal in 10,000 animals, including isolated reports), neurological signs such as blindness, ataxia, and recumbency may occur after administration of the product. These cases may also be associated with gastrointestinal signs such as anorexia, diarrhoea and in extreme cases signs may persist and may result in death of the animal.

Even though the overall incidence of adverse events is very rare, it has been noted that, when there is an adverse event in a herd, several animals may be affected. Therefore, should neurological signs be observed in one animal, it is recommended to reinforce surveillance, at the herd level, of all treated animals.

4.7 Use during pregnancy, lactation or lay

The product can be administered to cattle (including dairy beef/suckler cattle) at any stage of pregnancy or lactation provided that the milk is not intended for human consumption. See section 4.11.

4.8 Interaction with other medicinal products and other forms of interactions

None known.

4.9 Amounts to be administered and administration route

The veterinary medicinal product should be administered topically at a dosage rate of 500 microgram ivermectin per kg bodyweight and 20 mg closantel per kg bodyweight (1 ml per 10 kg).

The formulation should be applied along the midline of the back in a narrow strip between the withers and the tail head. Assess bodyweight carefully prior to administration.

The timing for treatment should be based on epidemiological factors and should be customised for each individual farm. A dosing programme should be established by a veterinary professional.

HANDY DOSING GUIDE		ANIMALS SHOULD BE WEIGHED AND GROUPED ACCORDING TO BODYWEIGHT TO AVOID UNDER OR OVER-DOSING*				
BODYWEIGHT	DOSE VOLUME	NUMBER OF FULL DOSES PER PACK				
		250 ml	500 ml	1 litre	2.5 litre	5 litre
100 kg*	10 ml	25	50	100	250	500
150 kg	15 ml	16	33	66	166	333
200 kg	20 ml	12	25	50	125	250
250 kg	25 ml	10	20	40	100	200
300 kg	30 ml	8	16	33	83	166
350 kg	35 ml	7	14	28	71	142

400 kg	40 ml	6	12	25	62	125
450 kg	45 ml	5	11	22	55	111
500 kg	50 ml	5	10	20	50	100
550 kg	55 ml	4	9	18	45	90
600 kg	60 ml	4	8	16	41	83

* Dose rate 1 ml per 10 kg bodyweight

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

At doses of three times the recommended dose, no significant clinical signs were recorded.

Ivermectin

No antidote has been identified. Symptomatic treatment may be beneficial.

Closantel like other salicylanilides is a potent uncoupler of oxidative phosphorylation and the safety index is not as high as is the case of many other anthelmintics. However where used as directed there are unlikely to be any untoward effects. Signs of overdosage can include slight loss of appetite, loose faeces, decreased vision and increased frequency of defecation. High doses may cause blindness, hyperventilation, general weakness and inco-ordination, hyperthermia, convulsions, tachycardia and in extreme cases death. Treatment of overdosage is symptomatic as no antidote has been identified.

4.11 Withdrawal period(s)

Meat and offal: 58 days

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the second half of pregnancy in heifers which are intended to produce milk for human consumption.

Due to the significant likelihood of cross-contamination of non-treated animals with this product due to grooming (licking), all animals in a group should be treated at the same time and treated animals should be kept separately from non-treated animals throughout the withdrawal period. Non-compliance with this recommendation may lead to residues violations in non-treated animals.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

ATCvet Code: QP54AA51

Pharmacotherapeutic Group: Ivermectin, combinations.

5.1 Pharmacodynamic properties

Ivermectin is an endectocide with activity against a wide range of internal and external parasites. Ivermectin is a macrocyclic lactone and acts by inhibiting nerve impulses. It binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane

to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the relevant parasites. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels. The macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Closantel is a member of the salicylanilide class of anthelmintics. Salicylanilides are hydrogen (proton) ionophores (referred to as oxidative phosphorylase uncouplers.)

The chemical structure of salicylanilides illustrate the possession of a detachable proton. This type of molecule is lipophilic and is known to shuttle protons across membranes, in particular the inner mitochondrial membrane. Closantel acts by uncoupling oxidative phosphorylation.

Closantel is a parasiticide with flukicide activity and efficacy against certain other helminths and arthropods.

5.2 Pharmacokinetic particulars

After topical administration of Closivet Pour-On to cattle at a dose rate of 500 µg ivermectin per kg and 20 mg closantel per kg the following parameters were observed: Ivermectin – Cmax of 19.13 ng/mL and AUC of 2440 ng.hr/mL; Closantel – Cmax of 68.5 µg/mL and AUC of 35207 µg.hr/mL.

Ivermectin is only partially metabolised. In cattle, only about 1 to 2% is excreted in the urine the remainder is excreted in the faeces, approximately 60% of which is excreted as unaltered drug. The remainder is excreted as metabolites or degradation products. Salicylanilides are poorly metabolised and are excreted mainly unchanged. About 90% of closantel is excreted unchanged in the faeces and urine in cattle.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Brilliant Blue FCF (E133) Dye
Anhydrous Ethanol
Macrogol
Cetearyl Ethylhexanoate
Isopropyl Myristate
Povidone
Denatonium Benzoate
Trolamine
Isopropyl alcohol

6.2 Major incompatibilities

None known.

6.3 Shelf-life

Shelf-life of the veterinary medicinal product as packaged for sale: 18 months

6.4 Special precautions for storage

Do not store above 25°C.

Store upright in original container.

Protect from light.

If stored at temperatures below 0°C, the product may appear cloudy. Allowing to warm at room temperature will restore the normal appearance without affecting efficacy.

Flammable – keep away from heat, sparks, open flame or other sources of ignition.

6.5 Nature and composition of immediate packaging

Translucent 250 mL, 500 mL and 1 L HDPE containers with white HDPE caps, white 1 L, 2.5 L and 5 L HDPE backpacks with white polypropylene screw caps and a 4 L combination pack with dosing gun. The 4 L combination pack comprises of 500 ml container, 1 L container or back pack and 2.5 L backpack.

Not all packs 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

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container. Any unused product or waste material should be disposed of in accordance with national requirements.

7 MARKETING AUTHORISATION HOLDER

Norbrook Laboratories (Ireland) Limited
Rossmore Industrial Estate
Monaghan
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

VPA22664/102/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2012
Date of latest renewal: 21 July 2017

10 DATE OF REVISION OF THE TEXT

November 2021