

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Closiver 5 mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the product contains:

Active Substances :

Ivermectin	5 mg
Closantel (as closantel sodium dihydrate) (equivalent to 135,9 mg of closantel sodium dihydrate)	125 mg

Excipients :

Sodium Formaldehyde Sulphoxylate	5 mg
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For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear amber solution.

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle and Sheep.

4.2 Indications for use, specifying the target species

Cattle:

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

Gastrointestinal roundworms

Ostertagia ostertagi (including inhibited larval stages), *Ostertagia lyrata* (adult), *Haemonchus placei* (adult and immature), *Trichostrongylus axei* (adult and immature), *Trichostrongylus colubriformis* (adult and immature), *Cooperia oncophora* (adult and immature), *Cooperia punctata* (adult and immature), *Cooperia pectinata* (adult and immature), *Oesophagostomum radiatum* (adult and immature), *Nematodirus helvetianus* (adult), *Nematodirus spathiger* (adult), *Strongyloides papillosus* (adult), *Bunostomum phlebotomum* (adult and immature), *Toxocara vitulorum* (adult), *Trichuris* spp.

Lungworms

Dictyocaulus viviparus (adult and 4th stage larvae)

Liver Fluke (trematodes)

Fasciola gigantica, *Fasciola hepatica*

Treatment of fluke at 12 weeks (mature) > 99% efficacy.

Treatment of fluke from 7 weeks (late immature) > 90% efficacy.

Eyeworms (adult)

Thelazia spp

Cattle grubs (parasitic stages)

Hypoderma bovis, *Hypoderma lineatum*

Lice

Linognathus vituli, *Haematopinus eurysternus*, *Solenopotes capillatus*

Mange Mites

Psoroptes ovis (syn *P. communis varbovis*), *Sarcoptes scabiei var bovis*

The veterinary medicinal product may also be used as an aid in the control of the biting louse *Damalinia bovis* and the mange mite *Chorioptes bovis*, but complete elimination may not occur.

Sheep:

For the treatment of mixed trematode (flake) and nematode or arthropod infestations due to gastrointestinal roundworms, trematodes, lungworms, nasal bots and mites of sheep.

Gastrointestinal roundworms

Teladorsagia circumcincta (including inhibited L4), *Teladorsagia trifurcata* (adult and L4), *Haemonchus contortus* (including inhibited L4), *Trichostrongylus axei* (adult), *Trichostrongylus colubriformis* (adult and L4), *T. vitrinus* (adult) *Cooperia curticei* (adult and L4), *Oesophagostomum columbianum* (adult and L4), *O. venulosum* (adult) *Chabertia ovina* (adult and L4) *Nematodirus filicollis* (adult and L4), *Trichuris ovis* (adult).

[L4 = fourth stage larvae]

Lungworms

Dictyocaulus filaria (adult and 4th stage larvae)

Protostrongylus rufescens (adult)

Liver Fluke (Adults and 7 weeks immature)

Fasciola gigantica, *Fasciola hepatica*

Nasal Bots

Oestrus ovis

Mange Mites

Psoroptes ovis (Treatment requires a second injection of an ivermectin-only product 7 days later. See sections 4.4 and 4.9)

Benzimidazole – resistant strains of *Haemonchus contortus* and *Teladorsagia circumcincta* are also controlled.

4.3 Contraindications

Do not use by intramuscular or intravenous route.

Do not use in animals with known hypersensitivity to the active substance(s) or to any of the excipients.

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

Please refer to Section 4.7 and 4.8 of the SPC.

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.

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 and there have also been isolated geographical reports of resistance in *Ostertagia ostertagi* in cattle. Therefore the use of this product should be based on local epidemiological information about the susceptibility of the *Cooperia* spp and *Ostertagia* spp and recommendations on how to limit further selection for resistance to anthelmintics.

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

In sheep treatment of psoroptic mange (sheep scab) with one injection of this product will not be effective in eliminating all the mites. A suitable ivermectin-only injectable product must be administered seven days after the treatment with this product to treat clinical signs and to eliminate the mites.

Sheep scab (*Psoroptes ovis*) is an extremely contagious external parasite of sheep. To ensure complete control great care must be taken to avoid re-infestation, as mites may be viable for up to 15 days off the sheep. It is important that all sheep which have been in contact with infected sheep are treated with an appropriate product. Contact between treated, infected and untreated flocks must be avoided until at least seven days after treatment.

4.5 Special precautions for use

Special precautions for use in animals

Doses of more than 10 ml should be injected in two different sites in order to reduce the transitory discomfort or reactions at the injection site.

Due to the potential for secondary reactions due to death of *Hypoderma* larvae, it is not advisable to administer the product when *Hypoderma lineatum* larvae are localised in the periaesophagic region, or when *Hypoderma bovis* larvae are situated in the spinal canal. Seek the advice of your veterinarian to determine the best period of use.

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

Do not smoke, eat or drink while handling the product.

Avoid direct contact of the product with the skin. In case of spillage onto the skin rinse immediately with fresh water.

Wash hands after use.

Take care to avoid self-injection. Inadvertent self-injection may result in local irritation and/or pain at the injection site.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet to the physician.

Other Precautions

Ivermectin is very toxic to aquatic organisms and dung insects. Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment. Long term effects on dung insects caused by continuous or repeated use cannot be excluded. Therefore repeated treatment of animals on a pasture with an ivermectin-containing product within a season should only be given in the absence of alternative treatments or approaches to maintain animal/flock health, as advised by a veterinarian.

4.6 Adverse reactions (frequency and seriousness)

Tissue swellings at the injection site, which can cause transitory discomfort in cattle are common up to 48 hours after injection which resolve thereafter without treatment. Hardness on palpation may be observed up to 7 days following administration.

Transitory swelling has rarely been observed in sheep at the injection site and occasionally this swelling is accompanied by pain and discomfort. This swelling resolves completely within 14 days following treatment.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)

- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

4.7 Use during pregnancy, lactation or lay

The veterinary medicinal product can be administered to cattle and sheep at any stage of pregnancy or lactation provided that the milk is not intended for human consumption.

Before use in dairy animals see Section 4.11.

4.8 Interaction with other medicinal products and other forms of interactions

Do not administer concomitantly with chlorinated compounds. The effect of GABA agonists are increased by ivermectin.

4.9 Amounts to be administered and administration route

The veterinary medicinal product should be administered at a dosage rate of 200 µg ivermectin per kg bodyweight and 5 mg closantel per kg bodyweight (1 ml per 25 kg). It should only be injected subcutaneously into the neck. A maximum dose of 10 ml should be administered at any one site with any residual volume administered at another site in the neck. A sterile 16-gauge, one-inch needle is recommended.

Assess bodyweight carefully prior to administration.

This product does not contain an antimicrobial preservative. Swab septum before removing each dose. Use a dry sterile needle and syringe. For 250 ml and 500 ml pack sizes, use of a multiple dose syringe is recommended. To refill the syringe, use of a draw-off needle is recommended to avoid excessive broaching of the stopper.

Do not exceed 40 broachings per vial. If more than 40 broachings are required, use of a draw off needle is recommended.

The timing for treatment should be based on epidemiological factors and should be customised for each individual farm. Professional veterinary advice should be sought on appropriate dosing programmes and stock management to achieve adequate parasite control and reduce the likelihood of resistance developing.

To ensure administration of a correct dose, bodyweight should be determined as accurately as possible; accuracy of the dosing device should be checked.

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 overdosing.

For the treatment and control of sheep scab an injection of the veterinary medicinal product may be administered but must be followed with a second injection of an ivermectin only product seven days after the initial injection to treat clinical signs of scab and to eliminate mites. This injection should be administered at the other side of the neck.

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

Dose levels approaching 4.0 mg/kg ivermectin (20 times the recommended dosage) administered subcutaneously, result in ataxia and depression in cattle and sheep.

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 loss of appetite, decreased vision, loose faeces and increased frequency of defaecation. High doses may cause blindness, hyperventilation, hyperthermia, general weakness, inco-ordination, convulsions, tachycardia and in extreme cases death.

No antidote has been identified for either ivermectin or closantel overdosage. Symptomatic treatment may be beneficial.

Oral closantel doses in excess of 82.5 mg/kg in cattle may cause blindness, hyperventilation, hyperthermia, general weakness, incoordination, convulsions, tachycardia and in extreme cases, death.

Following intramuscular administration of closantel in acute toxicity studies, the first deaths in cattle were noted at 35 mg/kg.

The lethal dose (LD₅₀) of closantel in sheep, after a single intramuscular dose, was higher than 40 mg/kg. Moreover, some studies conducted in sheep reported signs of overdose with doses of around 4 times the therapeutic dose (both injectable and oral).

4.11 Withdrawal period(s)

Cattle:

Meat and offal: 49 days.

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

Sheep:

Meat and offal: 28 days.

Milk: 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.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endectocides, Macrocyclic lactones, Avermectins, ivermectin, combinations.

ATCvet code: QP54AA51

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.

Resistance to macrocyclic lactones has been reported in *Teladorsagia* and *Trichostrongylus* in sheep in a number of countries. In cattle resistance to macrocyclic lactones (MLs) has been reported mainly with *Cooperia oncophora* in some European countries. Therefore the use of this medicinal product should be based on local (regional, farm) epidemiological information about susceptibility of parasites, local history of treatments and recommendations on how to use the medicinal product under sustainable conditions to limit further selection for anthelmintic resistance.

P-glycoproteins (Pgps) have been frequently implicated in ivermectin resistance and are a major cause of multi-drug resistance in protozoa and helminths.

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. Treatment with the veterinary medicinal product when fluke are five weeks and greater has been shown to reduce subsequent reproductive capacity and egg shedding.

5.2 Pharmacokinetic particulars

Cattle:

After subcutaneous administration of the veterinary medicinal product to cattle at a dose rate of 200 ug ivermectin per kg and 5mg closantel per kg the following parameters were observed: Ivermectin C_{max} of 57.3 ng/ml and AUC of 7106 ng.hr/ml; Closantel C_{max} of 63.4 ug/ml and AUC of 21996 ug.hr/ml. Ivermectin is only partially metabolised. In cattle, only about 1-2 % 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. Closantel is extensively bound to plasma protein. About 90 % of closantel is excreted unchanged in the faeces and urine in cattle.

Sheep:

After subcutaneous administration of the veterinary medicinal product at a dose rate of 200 µg ivermectin per kg and 5mg closantel per kg the following parameters were observed: Ivermectin Cmax of 24.52 ng/ml and AUC of 2082.93 ng.h/ml;

Closantel Cmax of 70.4 µg/ml and AUC of 41043 µg.h/ml.

Ivermectin binds extensively to plasma proteins. Due to its high lipophilic nature, ivermectin is extensively distributed. It tends to accumulate in fat tissue, which acts as a drug reservoir and the highest levels of ivermectin are found in liver and fat. Ivermectin is only partially metabolised. Ivermectin is mainly eliminated in the faeces as unaltered drug and faecal excretion accounts for 90 % of the dose administered with <2 % of the dose excreted in urine. Ivermectin is also excreted by the mammary gland.

Salicylanilides are poorly metabolised and are excreted mainly unchanged. The main excretion route is the faeces via the bile. Closantel is extensively bound to plasma proteins, almost exclusively to albumin. The distribution to tissues is poor. Closantel has a long elimination half-life.

5.3 Environmental Properties

The long term effect of ivermectin and closantel on the population dynamics of the dung beetle has not been investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Formaldehyde Sulphoxylate
Povidone K12
Macrogol 200
Glycerol Formal

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf-life

Shelf-life of the veterinary product as packaged for sales: 18 months.
Shelf-life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage

Do not store above 25°C. Protect from light.

6.5 Nature and composition of immediate packaging

100 ml, 250 ml and 500 ml Type 1 glass multidose vials and aluminium caps complete with bromobutyl bungs and aluminium seals.
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

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norbrook Laboratories (Ireland) Limited
Rossmore Industrial Estate
Monaghan
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8 MARKETING AUTHORISATION NUMBER(S)

VPA22664/084/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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