

# Summary of Product Characteristics

## 1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Closamectin Solution for Injection for Cattle and Sheep

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Ivermectin	5	mg
Closantel (as Closantel Sodium Dihydrate)	125	mg

Excipients:

Sodium Formaldehyde Sulphoxylate	5	mg
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For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.

A clear amber solution free from visible particles.

## 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 gastrointestinal roundworms, lungworms, eyeworms, warbles, mites and lice of cattle.

#### 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 4<sup>th</sup> 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 eurytenuis*, *Solenopotes capillatus*

Mange Mites

*Psoroptes ovis* (*synP communis varbovis*), *Sarcoptes scabiei var bovis*

Closamectin Injection may also be used as an aid in the control of the biting louse *Damalinea bovis* and the mange mite *Chorioptes bovis*, but complete elimination may not occur.

Persistent activity in cattle

When cattle have to graze on pasture contaminated with infective larvae of cattle nematodes, treatment with Closamectin Injection at the recommended dose rate of 200 µg ivermectin per kg bodyweight and 5 mg closantel per kg bodyweight controls re-infection with:

**Prolonged activity**

<i>Dictyocaulus viviparus</i>	Up to 21 days
<i>Ostertagia ostertagi</i>	Up to 21 days
<i>Oesophagostomum radiatum</i>	Up to 21 days
<i>Cooperia</i> spp	Up to 14 days
<i>Trichostrongylus axei</i>	Up to 14 days
<i>Haemonchus placei</i>	Up to 14 days

**Sheep:**

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

Gastrointestinal roundworms

*Ostertagia circumcincta* (including inhibited L4), *Ostertagia 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 4<sup>th</sup> stage larvae)  
*Protostrongylus rufescens* (adult)

Liver Fluke (trematodes)

*Fasciola gigantica*, *Fasciola hepatica*

Treatment of fluke at 12 weeks (mature) >95% efficacy.  
Treatment of fluke at 7 weeks (late immature) 100% efficacy.

Nasal Bots

*Oestrus ovis*

Mange Mites

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

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

**4.3 Contraindications**

Closamectin Injection is not for intravenous or intramuscular use.

Avermectins may not be well tolerated in all 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).

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

#### 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. 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.

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

##### (i) Special precautions for use in animals

None.

##### (ii) 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.

##### (iii) 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)

Transitory discomfort has been observed in some cattle following subcutaneous administration. Tissue swellings at the injection site 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 occasionally been observed in sheep at the injection site. Occasionally this swelling is accompanied by pain and discomfort. This swelling completely resolves within 14 days of treatment.

#### **4.7 Use during pregnancy, lactation or lay**

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

#### **4.8 Interaction with other medicinal products and other forms of interactions**

Do not administer concomitantly with chlorinated compounds. The effects of GABA agonists are increased by ivermectin. Please refer to section 4.3 of the SPC.

#### **4.9 Amounts to be administered and administration route**

Closamectin Injection should be administered at a dosage rate of 200 microgram 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.

For the treatment and control of sheep scab an injection of Closamectin Injection for Sheep 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.

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. As with other anthelmintics, 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 over-dosing.

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

Single doses of 4.0 mg/kg ivermectin (20 times the recommended dosage) administered subcutaneously, result in ataxia and depression. 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 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. Treatment of overdosage is symptomatic as no antidote has been identified.

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

#### **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

ATCvet code: QP54AA51

Pharmacotherapeutic group: Anthelmintic.

### 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. Treatment with Closamectin 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 Closamectin Injection to cattle at a dose rate of 200 microgram ivermectin per kg and 5 mg 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 microgram/ml and AUC of 21996 microgram.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. About 90 % of closantel is excreted unchanged in the faeces and urine in cattle.

#### Sheep:

After subcutaneous administration of Closamectin Injection to sheep at a dose rate of 200 microgram ivermectin per kg and 5 mg closantel per kg the following parameters were observed: Ivermectin  $C_{max}$  of 24.52 ng/ml and AUC of 2082.93 ng.h/ml;

Closantel  $C_{max}$  of 70.4 microgram/ml and AUC of 41043 microgram.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.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Povidone K12  
Sodium Formaldehyde Sulphoxylate  
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 sale: 18 months.  
Shelf-life after first opening of immediate packaging: 28 days.

### **6.4 Special precautions for storage**

Do not store above 25°C.  
Protect from light.  
Discard unused material.

### **6.5 Nature and composition of immediate packaging**

100 ml, 250 ml and 500 ml 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 products should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Norbrook Laboratories (Ireland) Limited  
Rossmore Industrial Estate  
Monaghan  
Ireland

## **8 MARKETING AUTHORISATION NUMBER(S)**

VPA22664/083/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 09 November 2007  
Date of last renewal: 27 April 2012

## **10 DATE OF REVISION OF THE TEXT**

January 2019