Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Closiver 5 mg/ml + 125 mg/ml Solution for Injection for Sheep

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active Substance:

Ivermectin	5 mg
Closantel	125 mg
(Equivalent to Closantel sodium dihydrate)	135.9 mg

Excipients:

Sodium formaldehyde sulphoxylate	5 mg

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

Sheep.

4.2 Indications for use, specifying the target species

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
Teladorsagia 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^{th} 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 intravenously or intramuscularly.

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

Resistance to macrocyclic lactones has been reported in *Trichostrongylus* in sheep in a number of countries.
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

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).

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

Do not smoke, eat or drink while handling the product.
Direct contact of the product with the skin should be kept to a minimum. 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 label or package leaflet to the physician.

4.6 Adverse reactions (frequency and seriousness)

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

4.7 Use during pregnancy, lactation or lay

The product can be administered to sheep 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 interaction

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

4.9 Amounts to be administered and administration route

The 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 beinjected subcutaneously into the neck. A sterile 16-gauge, one-inch needle is recommended.

For the treatment and control of sheep scab an injection of the 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.

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

Dose levels up to 4.0 mg/kg ivermectin (20 times the recommended dosage) administered subcutaneously, result in ataxia and depression in 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, incoordination, convulsions, tachycardia and in extreme cases death. The lethal dose (LD_{50}) 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). Treatment of over dosage is symptomatic as no antidote has been identified.

4.11 Withdrawal Period(s)

Meat and offal: 28 days

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: Endectocides, Macrocyclic lactones, Avermectins, ivermectin, combinations

5.1 Pharmacodynamic properties

Ivermectin is an endectocide with activity against a wide range of internal and external parasites. Ivermectin is a macrocylic 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 macrocylic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

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.

5.2 Pharmacokinetic properties

After subcutaneous administration of the product to sheep at a dose rate of 200 µg ivermectin per kg and 5 mg 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K12
Sodium Formaldehyde Sulphoxylate
Macrogol 200
Glycerol Formal

6.2 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.

6.5 Nature and composition of immediate packaging

100 ml, 250 ml and 500 ml Type I 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

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 materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norbrook Laboratories Limited
Station Works
Camlough Road
Newry
Co Down,
BT35 6JP
Northern Ireland

8 MARKETING AUTHORISATION NUMBER(S)

VPA: 10999/126/001

9 DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010
Date of last renewal: 18th September 2015

10 DATE OF REVISION OF THE TEXT