SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Closiver 5mg/ml + 200mg/ml Pour-On Solution for Cattle (UK)
Closamectin Vet 5mg/ml + 200mg/ml Pour-On Solution for Cattle (SE)
Closamectin 5mg/ml + 200mg/ml Pour-On Solution for Cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active Ingredient(s)

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

Excipients

Brilliant Blue FCF (E133)	0.1 mg

For a 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.

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.

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

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.

Do not use the product between December and March in those countries in which *Hypoderma* spp have not been eradicated as killed larvae may cause hypersensitivity reactions.

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

The presence of liver fluke or *Haemonchus* infestation should be confirmed before this combination product is used.

If treatment against liver fluke infestation only is required, a single active substance product should be used.

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 for up to 48 hours 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 (an avermectin) has been reported in *Cooperia oncophora* in cattle within the EU. Therefore the use of this product should be based on local (regional and farm) epidemiological information about susceptibility of the gastrointestinal nematodes 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

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

This product may be irritating to human skin and eyes or cause hypersensitivity. Avoid skin and/or eye contact with the product during treatment, when handling recently treated animals or when cleaning the used equipment. 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.

This product may be toxic after accidental ingestion. Avoid ingestion by hand-to-mouth contact. Do not eat, drink or smoke whilst handling the product. If accidental ingestion occurs, get medical attention and show the package leaflet to the physician. Wash hands after use.

This product is flammable. Keep away from sources of ignition. Use only in well ventilated areas or outdoors.

iii. Other Precautions Regarding the Environment

The product 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 repeat treatments on a pasture within a season should only be given on the advice of a veterinarian.

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

Closiver Pour-On 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 Interactions with Other Medicinal Products and Other Forms of Interaction

Do not combine ivermectin treatment with vaccination against lungworms. If vaccinated animals are to be treated, treatment should not be carried out within a period of 28 days before or after vaccination.

4.9 Amounts to be Administered and Administration Route

Pour-on use.

The veterinary medicinal product should be administered topically at a dosage rate of 500 μg 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.

To ensure administration of a correct dose, body weight 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.

The timing for treatment should be based on local epidemiological factors and should be customised for each individual farm. A comprehensive parasite control programme should be established by a veterinary professional. It should be confirmed that mixed infestations are present before the product is prescribed.

The efficacy profile of the product is such that a single treatment seven weeks after housing will control infestation for the entire housed period.

The product should not be repeatedly applied (within 7 weeks) to cattle.

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				
		250ml	500ml	1 litre	2.5 litre	5 litre
100kg*	10ml	25	50	100	250	500
150kg	15ml	16	33	66	166	333
200kg	20ml	12	25	50	125	250
250kg	25ml	10	20	40	100	200
300kg	30ml	8	16	33	83	166
350kg	35ml	7	14	28	71	142
400kg	40ml	6	12	25	62	125
450kg	45ml	5	11	22	55	111
500kg	50ml	5	10	20	50	100
550kg	55ml	4	9	18	45	90
600kg	60ml	4	8	16	41	83

* Dose rate 1ml per 10kg bodyweight

4.10 Overdose (Symptoms, Emergency Procedures and 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 Periods

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 PROPERTIES

Pharmacotherapeutic Group: Ivermectin, combinations.

ATC Vet Code: QP54AA51

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.

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 topical administration of Closiver 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 Excipient(s)

Brilliant Blue FCF (E133) Dye
Anhydrous Ethanol
Macrogol 200
Cetearyl Ethylhexanoate
Isopropyl Myristate
Povidone K30
Denatonium Benzoate
Trolamine
Isopropyl alcohol

6.2 Incompatibilities

None known.

6.3 Shelf-Life

Shelf-life of the veterinary medicinal product is 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.
Discard unused material. Avoid introduction of contamination.
Replace the cap securely after use.
If stored at temperatures below 0°C, Closiver Pour-On Solution for Cattle may appear cloudy. Allowing to warm at room temperature will restore the normal appearance without affecting efficacy.
Accidental spillage or ingestion could be detrimental or even fatal therefore care should be taken when handling and storing this product.

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

6.5 Nature and Composition of Immediate Packaging

Translucent 250 mL, 500mL and 1L HDPE containers with integral squeeze measure pour system and white HDPE caps.
White 1L, 2.5L and 5L HDPE backpacks for use with a dosing gun delivery system and white polypropylene screw caps.

Not all packs sizes may be marketed.

6.6 Special Precautions for the Disposal of Unused Veterinary Medicinal Product or Waste Materials Derived from the Use of Such Products, if appropriate

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

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BT35 6JP
Northern Ireland

8. MARKETING AUTHORISATION NUMBER

Vm 02000/4311

9. DATE OF FIRST AUTHORISATION

19 May 2011

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