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

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Brilliant Blue FCF (E133)	0.1 mg
Anhydrous Ethanol	
Macrogol	
Cetearyl Ethylhexanoate	
Isopropyl Myristate	
Povidone	
Denatonium Benzoate	
Trolamine	
Isopropyl alcohol	

A clear blue/green solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle.

3.2 Indications for use for each 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*

3.3 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.

3.4 Special warnings

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.

3.5 Special precautions for use

Special precautions for safe use in the target species

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 3.12) or in very rare cases, it can lead to adverse events (see section 3.6) 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.

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. Personal protective equipment consisting of nitrile rubber gloves and boots with a waterproof coat should be worn 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.

Special precautions for the protection of the environment

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

Other precautions
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).

3.6 Adverse events

Cattle.

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Neurological signs[1],(e.g. Ataxia, Blindness, Recumbency) Gastrointestinal signs (e.g. Anorexia, Diarrhoea) Death[2]

[1] When there is an adverse event in a herd, several animals may be affected. Should neurological signs be observed in one animal, it is recommended to reinforce surveillance, at the herd level, of all treated animals.
[2] In extreme cases.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation
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.

3.8 Interactions with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

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 a correct dosage, body weight should be determined as accurately as possible.

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				
		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

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance.

Not applicable.

3.12 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.

4. PHARMACOLOGICAL or IMMUNOLOGICAL INFORMATION

4.1 ATC Vet Code: QP54AA51

4.2 Pharmacodynamics

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 hyperpolarisation 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.

4.3 Pharmacokinetics

After topical administration of the veterinary medicinal product at a dose rate of 500 µg ivermectin per kg and 20 mg closantel per kg the following parameters were observed: Ivermectin – C_{max} of 19.13 ng/mL and AUC of 2440 ng.hr/mL; Closantel – C_{max} 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

None known.

5.2 Shelf life

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

5.3 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.

5.4 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 backpack and 2.5 L backpack.

Not all packs sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

The veterinary medicinal product should not enter water courses as ivermectin is extremely dangerous for fish and other aquatic organisms.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Norbrook Laboratories (Ireland) Limited

7. MARKETING AUTHORISATION NUMBER(S)

VPA22664/102/001

8. DATE OF FIRST AUTHORISATION

25/05/2012

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

06/06/2024

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).