BASE VIAL LABEL TEXT

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES / 3. PHARMACEUTICAL FORM

A solution for injection containing 5 mg/ml ivermectin and 125 mg/ml closantel.
Antioxidant: sodium formaldehyde sulphoxylate 5 mg/ml

A clear amber solution.

4. PACKAGE SIZE

100ml
250ml
500ml

5. TARGET SPECIES

Sheep

6. INDICATIONS

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

7. METHOD AND ROUTES OF ADMINISTRATION

Inject subcutaneously at a dosage rate of 0.2mg ivermectin/kg bodyweight and 5mg closantel/kg bodyweight (1ml per 25kg), into the neck. A sterile 16-gauge, one-inch needle is recommended.

8. WITHDRAWAL PERIOD

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.

9. SPECIAL WARNING(S), IF NECESSARY

Do not use intravenously or intramuscularly. Should any apparent growth or discoloration occur the product should be discarded. This product does not contain an antimicrobial preservative.

USER WARNINGS:
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 package label to the physician.

IMPORTANT – READ EXPANDING LABEL BEFORE USE.

10. EXPIRY DATE

EXP {XX/XX/XXXX}
Shelf-life after first opening the immediate packaging: 28 days
Once broached use by……..

11. SPECIAL STORAGE CONDITIONS

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

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container. Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For Animal Treatment Only.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Norbrook Laboratories Limited
Newry
Northern Ireland

16. MARKETING AUTHORISATION NUMBER(S)

ManA 2000

17. MANUFACTURER'S BATCH NUMBER

XXXX-XX

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Carnbane Industrial Estate
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EXPANDING VIAL LABEL TEXT – PAGE 1

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

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A solution for injection containing 5 mg/ml ivermectin and 125 mg/ml closantel.
Antioxidant: sodium formaldehyde sulphoxylate 5 mg/ml

A clear amber solution.

4. PACKAGE SIZE

100ml
250ml
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5. TARGET SPECIES

Sheep

6. INDICATION(S)

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

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Inject subcutaneously at a dosage rate of 0.2mg ivermectin/kg bodyweight and 5mg closantel/kg bodyweight (1ml per 25kg), into the neck. A sterile 16-gauge, one-inch needle is recommended.

8. WITHDRAWAL PERIOD

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.

9. SPECIAL WARNING(S), IF NECESSARY

Do not use intravenously or intramuscularly. Should any apparent growth or discoloration occur the product should be discarded. This product does not contain an antimicrobial preservative.

USER WARNINGS:
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 package label to the physician.

IMPORTANT – READ EXPANDING LABEL BEFORE USE.

10. EXPIRY DATE

EXP {XX/XX/XXXX}
Shelf-life after first opening the immediate packaging: 28 days
Once broached use by……..

11. SPECIAL STORAGE CONDITIONS

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

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

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Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Norbrook Laboratories Limited
Newry
Northern Ireland

16. MARKETING AUTHORISATION NUMBER(S)

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EXPANDING VIAL LABEL TEXT – PAGES 2 TO 5

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing Authorisation Holder and manufacturer responsible for batch release:
Norbrook Laboratories Limited
Newry
Northern Ireland

Patent No:
EP1478327B

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

3. STATEMENT OF THE ACTIVE SUBSTANCES AND OTHER INGREDIENTS

A ready to use solution for injection containing 5 mg/mL ivermectin and 125 mg/mL closantel.
Antioxidant: sodium formaldehyde sulphoxylate 5 mg/ml

A clear amber solution.

4. INDICATION(S)

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 4th stage larvae)
Protostrongylus rufescens (adult)

Liver Fluke (trematodesAdults and 7 weeks immature)
Fasciola gigantica, Fasciola hepatica

Nasal Bots
Oestrus ovis

Mange Mites
Psoroptes ovis (Treatment require a second injection of an ivermectin-only product 7 days later. See section dosage for each species, routes and method of administration and special warnings.)

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

5. 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.

6. ADVERSE REACTIONS

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.
If you notice any serious effects or any other effects not mentioned in this leaflet, please inform your veterinary surgeon

7. TARGET SPECIES

Sheep.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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 be injected 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.

Bodyweight (Kg)	Volume (mL)
Up to 12.5	0.5
13.5 - 25	1.0
26 - 37.5	1.5
38.5 - 50	2.0
51 - 62.5	2.5
63.5 - 75	3.0

Over 75 kg bodyweight give 0.5 ml per 12.5 kg of bodyweight.

9. ADVICE ON CORRECT ADMINISTRATION

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.

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

10. WITHDRAWAL PERIOD

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.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 25°C.
Protect from light.

Use of a draw-off needle is recommended to avoid excess broaching of the stopper.
Shelf life after first opening the immediate packaging: 28 days. This date should be recorded on the label. Do not use after the expiry date stated on the label

12. SPECIAL WARNINGS

Special Warnings for Each Target Species:
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.

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.

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, inco-ordination, 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 overdosage is symptomatic as no antidote has been identified.

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).

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.

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

Interactions with Other Medicinal Products and Other Forms of Interaction:
Do not administer concomitantly with chlorinated compounds. The effect of GABA agonists are increased by ivermectin.

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.

For Animal Treatment Only.
Keep out of the sight and reach of children.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container. Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

October 2022

15. OTHER INFORMATION

ManA 2000

UK Only
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UK AUTHORISED VETERINARY MEDICINAL PRODUCT

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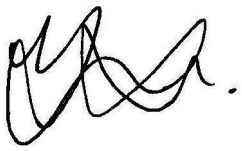
Package Quantities:
Multidose vials of 100 ml, 250 ml and 500 ml.
Not all pack sizes may be marketed.

MODE OF ACTION
Ivermectin paralyses and ultimately kills parasitic nematodes, arachnids and insects by its effect on the nervous system of these parasites. Ivermectin belongs to the avermectin class of anthelmintic endectocides. The mode of action exhibited by the avermectins is unique to this class of antiparasitic agents.

Closantel is a member of the salicylanilide class of anthelmintics. Salicylanilides are hydrogen ionophores which act as potent uncouplers of oxidative phosphorylation. The site of action of these proton ionophores is known to be selective uncoupling of oxidative phosphorylation in parasite mitochondria.



Approved: 28 October 2022