**IPAR**

**Publicly Available Assessment Report for a**
**Veterinary Medicinal Product**

Solantel 200 mg/ml Pour-on solution for cattle

**PRODUCT SUMMARY**

| | |
|---|---|
| EU Procedure number | IE/V/0552/002/DC |
| Name, strength and pharmaceutical form | Solantel 200 mg/ml Pour-On Solution for Cattle |
| Active substance(s) | Closantel |
| Applicant | Norbrook Laboratories Limited<br>Rossmore Industrial Estate<br>Monaghan<br>Ireland |
| Legal basis of application | Full dossier application in accordance with Article 12(3) of Directive 2001/82/EC as amended. |
| Date of completion of procedure | 31/03/2021 |
| Target species | Cattle |
| Indication for use | For the treatment of late immature (≥ 7 weeks) and adult *Fasciola hepatica* (fluke) infestations of cattle. |
| ATCvet code | QP52AG09 |
| Concerned Member States | UK(NI) |

**PUBLIC ASSESSMENT REPORT**

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

**I. SCIENTIFIC OVERVIEW**

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

**II. QUALITY ASPECTS**

***A. Qualitative and Quantitative Particulars***

The product contains 200 mg closantel (as closantel sodium dihydrate) and the excipients brilliant blue FCF (E133) dye, ethanol anhydrous, macrogol, cetearyl ethylhexanoate, isopropyl myristate, povidone, denatonium benzoate, trolamine, isopropyl alcohol
The container/closure system is white 1L, 2.5L and 5L HDPE backpacks for use with a suitable dosing device and white polypropylene screw caps.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

***B. Method of Preparation of the Product***

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

***C. Control of Starting Materials***

The active substance is closantel (as closantel sodium dihydrate), an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.
*Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies*
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

***D. Control on Intermediate Product***

Not applicable.

***E. Control Tests on the Finished Product***

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

***F. Stability***

Stability data on the active substances has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

***G. Other Information***

Not applicable.

## III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application is for Solantel 200mg/ml Pour-On Solution for Cattle containing closantel sodium dihydrate as the active substance. The application has been submitted via the decentralised procedure by Norbrook Laboratories Ltd., in accordance with paragraph 3 Article 12 of Directive 2001/82/EC, as amended (a full application).
The product is intended for administration to cattle for the treatment of late immature (> 7 weeks) and adult *Fasciola hepatica* (fluke) infestations. The product is formulated as a pour on solution containing 200 mg closantel per ml and intended for administration at a dose rate of 20 mg closantel per kg bodyweight (bw).

### III.A Safety Testing

***Pharmacological Studies***

Pharmacodynamics

The active substance, closantel is a salicylanilide anthelmintic. The basic mechanism of action is uncoupling of oxidative phosphorylation and metabolic disturbances of *Fasciola hepatica*. The pharmacodynamic properties of closantel have been adequately described using bibliographic evidence.

Pharmacokinetics

In support of the pharmacokinetic properties of closantel in the target species (cattle), the applicant has conducted a review of the pharmacokinetic data in the public domain and provided a proprietary GLP study investigating the pharmacokinetic profile of closantel following topical administration to cattle.
Based on published literature, studies have been conducted following oral and intramuscular administration of closantel in rats, mice, sheep and cattle. Results of these studies and the pivotal pharmacokinetic study conducted by the applicant demonstrate that closantel is highly protein bound, poorly metabolised, with a slow clearance rate and most of the dose given is eliminated unchanged in the faeces.

***Toxicological Studies***

A review of the published literature has been provided to characterise the toxicological profile of closantel. The data provided illustrates the following:

Single Dose Toxicity:

Studies have demonstrated that closantel has a reported $LD_{50}$ of 262 mg/kg bw in female rats. Acute intramuscular toxicity was reported at 28.4 mg/kg bw. The lowest reported $LD_{50}$ in sheep was 30 mg/kg orally and 40 mg/kg intramuscularly. The lowest reported $LD_{50}$ in cattle was >40 mg/kg orally and 35 mg/kg intramuscularly. The data indicates a relatively narrow acute toxicity safety range for sheep and cattle.

Repeated Dose Toxicity:

Epididymis effects were elicited at 2.5 mg/kg in the rat following repeated oral administration over 13 weeks. Toxic effects of closantel were noted in rats after subcutaneous administration, at doses of 6.25 mg/kg/day over 15 days. A No Observed Effect Level (NOEL) of 2.5 mg/kg has been established in Beagle dogs following oral dosing. Severe toxicity including irreversible blindness, was seen at a dose of 10 mg/kg following 3 subcutaneous injections in a Doberman Pinscher. Toxicity signs were seen at 20 mg/kg intramuscular injection in sheep. In cattle 68 mg/kg given orally was found to cause blindness.

Reproductive Toxicity, including Developmental Toxicity:

In rats administered 40 mg/kg orally monthly, reproductive effects were noted including reduced litter size and weight. At 10 mg/kg in the second generation, one male rat had a spermatic granuloma. No fertility effects were seen in bulls or rams given oral doses of 20 mg/kg orally on 3 occasions at 8 week intervals. No effect was seen in pregnancy rate, embryotoxic or teratogenic effects in ewes. In the repeat dose studies reported above, degeneration of the germinal epithelium was reported in sheep at the 20 mg/kg dose injected intramuscularly.

No foetotoxic, teratogenic or maternotoxic effects were observed in rats administered doses up to 40 mg/kg (oral), in rabbits administered doses up to 40 mg/kg bw (oral) nor in ewes administered doses up to 40 mg/kg bw (oral).

Genotoxicity:

The results of the Joint FAO/WHO Expert Committee (1991) and published literature on the genotoxicity of closantel determined that closantel does not appear to have genotoxic potential.

Carcinogenicity:

Based on data provided in the Joint FAO/WHO Expert Committee Report (1990) on closantel administered to rats for a period of 24 months at up to 40 mg/kg, haematopoietic tumours were seen in the 10 mg/kg dose and spermatic granulomas were reported. The NOEL was determined to be 2.5 mg/kg.

***Observations in Humans***

Closantel has been used in veterinary medicine for a number of years. It is not used in human medicine although there are reports in the literature of its use both intended and accidental in humans. Nausea and vomiting are noted following oral use at 2.5 mg/kg. Diarrhoea, drowsiness and blurred vision were noted at a dose of 5 mg/kg. The established toxicological ADI is 0.03 mg/kg bw i.e. 1.8 mg/person based on the NOEL of 2.5 mg/kg bw/day in rats and applying a safety factor of 100. Microbiological effects are not expected for this substance.

**User Safety**

The applicant provided a user safety assessment in compliance with the relevant guideline considering both the active substance closantel and the product excipients. Closantel is currently used in veterinary medicine. The applicant provided details of studies performed investigating the local effects of both the active substance and the final formulation for marketing. The studies demonstrated that the active substance, closantel, is a skin, ocular and inhalation irritant. The applicant provided information on the excipients included in the product and it was concluded a number of the excipients are considered to have sensitising potential and to be ocular, dermal and inhalation irritants. Therefore appropriate mitigation measures have been proposed. The user warnings in the SPC are considered adequate:

'*This product may be toxic after accidental ingestion. Avoid ingestion by hand-to-mouth contact. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.*

*This product may cause irritation to human skin and eyes.*

*This product may cause hypersensitivity (allergic) reactions in those known to be sensitised to polyethylene glycols (PEGs), povidones, isopropyl alcohol, triethanolamine, ethanol, and/or closantel.*

*Do not use in cases of known hypersensitivity to the active substance or to any of these excipients.*

*Avoid skin or eye contact with product.*

*Users should wear nitrile rubber gloves and boots with a waterproof coat when applying the product.*

*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 seek medical attention. Wash any exposed skin after use. Protective clothing should be washed after use.*

*This product is flammable.*

*Keep away from heat, sparks, open flame or other sources of ignition.*

*Store in a closed cabinet. Do not smoke or eat while handling the product.*

*This product contains volatile organic solvents, which may be accidentally inhaled.*

*Use only in well ventilated areas or outdoors.*'

Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product and the product is unlikely to present an unacceptable risk for the user when handled, used, stored and disposed of inaccordance with the recommendations included in the SPC.

**Environmental Risk Assessment**
The environmental risk assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.
***Phase I***
A Phase II ERA was required as the Phase I assessment showed that the product is an endoparasiticide for use in animals at pasture.

***Phase II Tier A***
A Phase II Tier A assessment was conducted, the results of which are summarised below:

| ***Physico-chemical properties*** | |
|---|---|
| **Study type** | **Result** |
| Vapour pressure | 1.2 x $10^{-16}$ Pa (25°C) |
| Water solubility | 2.7 mg/l |
| Dissociation constants in water pKa | pKa = 4.28 |
| n-Octanol/Water Partition Coefficient log$P_{ow}$ | log$P_{ow}$ = 4.96 (pH 9) |

| ***Environmental fate*** | |
|---|---|
| Soil Adsorption/Desorption | Koc = 162,181 |
| Aerobic and Anaerobic Transformation in Soil | $DT_{50}$ = 101.1 days (20°C) |

| ***Effect studies*** | | | |
|---|---|---|---|
| **Study type** | **Endpoint** | **Result** | **Unit** |
| Algae growth inhibition test/*Pseudokirchneriella subcapitata* | $EC_{50}$ | 1,000 | µg/l |
| *Daphnia* sp. immobilisation | $EC_{50}$ | 36.9 | µg/l |
| Fish, acute toxicity/*Oncorhynchus mykiss* | $LC_{50}$ | 25.6 | µg/l |
| Soil microorganisms: Nitrogen transformation test (28 days) | % effect | <25% | |
| Terrestrial Plants, growth test | $EC_{50}$ | 81 | mg/kg dry weight |
| Earthworm/*Eisenia fetida* reproduction | NOEC | 62.5 | mg/kg dry soil |
| Dung fly larvae/*species* | $EC_{50}$ | 467 | mg/kg dry weight |
| Dung beetle larvae/*Aphodius constans* | $LC_{50}$ | >1000 | mg/kg dry weight |
| Bioaccumulation in fish/*Oncorhyncus mykiss* | BMF | 0.012 | |

***Risk characterisation***
The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.
Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.
The risk characterisation resulted in risk quotients below 1 for the groundwater and soil compartments indicating that the product will not pose a risk to these compartments when used as recommended.
The results of the assessment for the surface water and dung compartments indicate that a risk for the environment potentially exists and consequently, risk mitigation measures are required for this product.

***PBT Assessment***
An assessment of the compound in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.
The log Kow of closantel was demonstrated to be 4.96.
The compound is not considered to be either PBT or vPvB.

***Conclusion***

The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.
Based on the data provided in the ERA, a risk to the aquatic and terrestrial environment cannot be excluded. Therefore suitable risk mitigation measures and advice were included in the SPC for this product.
'*This product is very toxic to aquatic organisms and dung insects.*
*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.*'

**III.B Residues Documentation**

***Residue Studies***

Residue depletion studies using the final formulation have been conducted in cattle. Samples of tissues were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period. The withdrawal period was established based on the statistical method incorporating a safety factor of 30%. The analytical method was performed with liquid chromatography-tandem mass spectrometry in compliance with the principles of GLP. The method was fully validated.

***MRLs***

Closantel is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

| Pharmacologically active substance | Marker residue | Animal species | MRL | Target tissues |
|---|---|---|---|---|
| Closantel | Closantel | Bovine | 1000 µg/kg<br>3000 µg/kg<br>1000 µg/kg<br>3000 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney |

***Withdrawal Periods***

Based on the data provided, a withdrawal period of 63 days for meat and offal in cattle is justified. This product is not authorised for use in cattle producing milk for human consumption, including during the dry period. It also should not be used during the second half of pregnancy in heifers which are intended to produce milk for human consumption.

**IV. CLINICAL ASSESSMENT**

**IV.A Pre-Clinical Studies**

***Pharmacology***

The active substance, closantel is a salicylanilide anthelmintic. The basic mechanism of action is uncoupling of oxidative phosphorylation and metabolic disturbances of *Fasciola hepatica*. The pharmacodynamic properties of closantel have been adequately described using bibliographic evidence.

***Tolerance in the Target Species of Animals***

The applicant conducted a target animal safety study, during which cattle were administered the product at up to 3 times the recommended daily dose. All doses were administered topically on 3 occasions 28 days apart. Tolerance was evaluated by clinical examinations, administration site evaluation, blood testing for biochemical and haematological parameters, and also bodyweight. Adverse effects observed during the study period were deemed to be sporadic in nature and unlikely to be treatment related. The study demonstrated that closantel was well tolerated in cattle when administered at up to 3 times the proposed dose. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

***Resistance***

Bibliographical data provided indicates there is little resistance to closantel by *Fasciola hepatica* and that the use of the proposed product will not produce a substantial increase in resistance to *Fasciola hepatica*. Furthermore, in view of the substantial increase in resistance to triclabendazole a further anthelminthic is needed to tackle fascioliasis. It was concluded that the product is unlikely to present an unacceptable risk for the user in relation to the development of resistance provided the product is used in accordance with the recommendations included in the SPC.

**IV.B Clinical Studies**

***Laboratory Trials***

The applicant conducted both dose determination and dose confirmation studies in cattle. The supportive dose determination study was provided. Three dose rates were investigated; 10 mg, 20 mg and 30 mg closantel/kg bodyweight against induced infections of late immature *Fasciola hepatica.* This study is considered adequate to support the dose investigated in the dose confirmatory studies. It is not considered a pivotal study as it has been conducted with the combined product Ivermectin/Closantel Pour-On.

The two pivotal dose confirmatory studies have demonstrated efficacy of the product against induced infections of late immature *Fasciola hepatica* (≥ 7 weeks) at a dose of 20 mg/kg. Cattle were allocated to the treatment group or placebo group. Helminth enumeration was conducted at time of slaughter blind relative to the treatment group. Efficacy was greater than 90% and a statistically significant difference was observed between the treatment and control groups. In addition, 3 further supportive dose confirmatory studies have been provided which also demonstrate efficacy at the proposed dose of 20 mg closantel/kg against late immature and adult fluke. These studies have been conducted with the combined ivermectin/closantel product and are therefore considered supportive only. The dose of 20 mg closantel/kg is considered adequately justified against late immature and adult *Fasciola hepatica* and confirmed as an appropriate posology to be investigated under field conditions.

***Field Trials***

The applicant conducted field studies which show that the product is both safe and effective for use in cattle. The pivotal field study evaluated the efficacy of the product as indicated, in cattle naturally infected with *Fasciola hepatica*. The study was GCP compliant, partially blinded, randomised, multisite field study. One group recieved a single (topical) administration of the product at the recommended dose rate (20 mg closantel per kg bodyweight). The other group received no treatment. Daily observations and adverse events were documented. No deviations in health condition and adverse events were observed. Individual rectal faecal samples of all animals were collected and analysed for the presence of liver fluke eggs. Efficacy of greater than 90% was demonstrated in addition to statistical difference between the treatment and control groups. The study can be accepted as confirming efficacy against *Fasciola hepatica* in the field.

A second, supportive study, used Ivermectin/Closantel Pour-On, a combination product. This study was conducted with a sample size of 10 calves in the treatment group and 10 in the control group. Following liver fluke enumeration post slaughter of the calves, efficacy of greater than 90% was demonstrated based on geometric mean counts and a statistical difference between the treatment and control groups was observed. The study can be considered to be supportive of the efficacy of the candidate product in the field.

Based on the data package provided the claim for efficacy of the candidate product against late immature and adult *Fasciola hepatica*, in field conditions has been adequately demonstrated and can be accepted.

## V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

## VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

**Changes:**

None.