**IPAR**

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

Santiola 50 mg/ml solution for injection for cattle and sheep

**PRODUCT SUMMARY**

| | |
|---|---|
| EU Procedure number | IE/V/0377/001/DC |
| Name, strength and pharmaceutical form | Santiola 50 mg/ml solution for injection for cattle and sheep |
| Active substance(s) | Closantel |
| Applicant | Krka, d.d., Novo mesto<br>Smarjeska cesta<br>Novo mesto 8501<br>Slovenia |
| Legal basis of application | Generic application in accordance with Article 13(1) of Directive 2001/82 as amended. |
| Date of Authorisation of procedure | |
| Target species | Cattle and sheep |
| Indication for use | For treatment of the following trematodes (fluke), gastro-intestinal nematodes and arthropods if sensitive to closantel.<br><br>***Sheep***<br>**Trematodes**<br>*Fasciola hepatica* (adult)<br>*Fasciola gigantica* (adult and 8 weeks immature)<br><br>**Nematodes**<br>*Haemonchus contortus* (adult and immature)<br>*Oesophagostomum columbianum* (adult and immature)<br>*Gaigeria pachyscelis* (adult and immature)<br>*Chabertia ovina* (adult and immature)<br><br>**Arthropods**<br>*Oestrus ovis* (1st, 2nd and 3rd instar)<br><br>***Cattle***<br>**Trematodes**<br>*Fasciola hepatica* (adult)<br>*Fasciola gigantica* (adult and 8 week immature)<br><br>**Nematodes**<br>*Haemonchus placei* (adult and immature)<br>*Bunostomum phlebotomum* (adult and immature)<br>*Oesophagostomum radiatum* (adult and immature)<br><br>**Arthropods**<br>*Hypoderma bovis* (dermal stages)<br>*Hypoderma lineatum* (dermal stages) |
| ATCvet code | QP52AG09 |
| Concerned Member States | BG, CZ, DK, EE, FR, HU, HR, LT, LV, RO, SE, SI, SK, UK |

**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 along with their expected frequency of occurrence.
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 50 mg/ml closantel (equivalent to 54.375 mg/ml closantel sodium dihydrate) and the excipients propylene glycol (E1520), povidone K 12, citric acid monohydrate, sodium hydroxide and water for injections.
The product is presented in type I amber glass vials closed with a bromobutyl rubber stopper.
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, an established 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 Products***

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 substance 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***

None

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

The application was made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). The reference product cited by the applicant was Flukiver 50 mg/ml Solution for Injection, marketed by Eli Lilly & Company Limited, Elanco Animal Health.

Exemption from the requirement for *in-vivo* bioequivalence studies was accepted in accordance with exemption 7.1 b) of the CVMP bioequivalence guideline. That is, the product has the same pharmaceutical form, contains the same concentration of the active substance and has the same excipients as the reference product. In addition, the product has the same indications for use in the same species and will be administered by the same route of administration at the same dose.

It was accepted that the candidate formulation is bioequivalent to the reference product without the need to conduct *in-vivo* bioequivalence studies.

As bioequivalence is accepted for the generic product and reference product, it follows that the safety profile will be similar with regards to target animal safety and user safety.

***III.A Safety Testing***

As this was a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests were not required.

***User Safety***

No user safety risk assessment was provided. However, it was highlighted that:

- The product has the same concentration of active substance and has the same excipients as the reference product;  It has the same indications for use in the same species;
- It will be administered by the same route of administration at the same dose.

- The tasks and situations that might lead to user exposure are not considered to differ between generic and reference products.

Consequently, it was accepted that the generic product and reference product can be used interchangeably, with a similar user safety profile. It was concluded that the generic product will not present an unacceptable risk for the user when stored, handled, used and disposed of in accordance with the recommendations proposed for inclusion in the SPC.

Warnings and precautions as listed on the product literature are consistent with those found on the reference product and are adequate to ensure safety to users of the product.

***Environmental Risk Assessment***

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

**Phase I:**

A Phase II ERA was required as the product is an ectoparasiticide and endoparasiticide for cattle and sheep and the target animals are reared on pasture.

**Phase II:**

A Phase II data set was provided on the active substance closantel according to the requirements of the CVMP/VICH guideline
GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the
VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). The data were considered to be acceptable.

| ***Physical-chemical properties*** | | |
|---|---|---|
| **Study type** | **Test protocol** | **Result** |
| Water solubility | OECD 105 | 31.7 µg/l |
| Dissociation constants in water pKa | OECD 112 | pKa = 6.36 for a phenol group |
| n-Octanol/Water Partition Coefficient $logP_{ow}$ | OECD 107 or 117 or 123 | $logK_{ow}$ at pH 5 = 4.5<br>$logK_{ow}$ at pH 7 = 3.9<br>$logK_{ow}$ at pH 9 = 4.0 |

| ***Environmental fate*** | | |
|---|---|---|
| Soil Adsorption/Desorption | OECD 106 | Koc = 18,249 $K_d$ = 330.4 |
| Aerobic and Anaerobic Transformation in Soil | OECD 307 | $DT_{50}$ = 183.8 days<br>$DT_{50,\ 12°C}$ =386.7 days |

| ***Effect studies*** | | | | |
|---|---|---|---|---|
| **Study type** | **Test protocol** | **Endpoint** | **Result** | **Unit** |
| Algae growth inhibition test/ *Raphidocelis subcapitata* | OECD 201 | $EC_{50}$ | 976.6 | µg/l |
| *Daphnia* sp. immobilisation | OECD 202 | $EC_{50}$ | 25.8 | µg/l |
| Fish, acute toxicity/ *Danio rerio* | OECD 203 | $LC_{50}$ | 38.9 | µg/l |
| Earthworm reproduction | OECD 222 | NOEC | 919 | $mg/kg_{dwt}$ |
| Dung fly larvae/ *Scathophaga stercoraria L.* | OECD 228 | $EC_{50}$ | 114.9 | $mg/kg_{wwt}$ |
| Dung beetle larvae/ *Aphodius constans* | OECD GD 122 | $LC_{50}$ | 1863.7 | $mg/kg_{wwt}$ |
| Bioaccumulation in fish/ *Danio rerio* | OECD 305 | BCF | 670.6 (kinetic, growth-corrected, lipid-normalised) | l/kg |

dwt = dry weight; wwt = wet weight

***Risk characterisation***

The risk characterisation resulted in a predicted exposure in groundwater of less than 0.1 µg/l and a risk quotient (RQ) below 1 for the soil compartment indicating that the product will not pose a risk to those compartments when used as recommended. The results of the assessment for the surface water and dung compartments indicate that a risk for the environment is indicated and that the following risk mitigation measures are required for this product:

Closantel is toxic to dung fauna.

To reduce the risk for the dung fauna, treated and untreated animals should be grazed on the same field.

In order to reduce the risk to aquatic organisms, treated animals should be kept out of water for at least 48 hours after treatment.

The following information on environmental properties needs to be included in the product literature:

Closantel has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of closantel may take place over a period of several weeks. Faeces containing closantel excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation. Closantel may affect aquatic organisms (aquatic invertebrates, sediment dwellers and fish).

**PBT assessment**

A PBT assessment was not required. In accordance with current guidance, as the BCF in an aquatic species was less than 2000, closantel does not fulfil the criteria for bioaccumulation.

### *III.B Residues Documentation*

#### *Residue Studies*

No residue depletion studies were conducted because the candidate formulation contains identical active and inactive ingredients as the reference product formulation and will be administered to the same target species, using the same route of administration and posology approved for the reference product. Consequently, it could be accepted that the rate of depletion of residues following administration of this generic product is not expected to differ from that of the reference product.

#### *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 | Other provisions |
|---|---|---|---|---|---|
| Closantel | Closantel | Bovine | 1000 µg/kg<br>3000 µg/kg<br>1000 µg/kg<br>3000 µg/kg<br>45 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney<br>Milk | No entry |
| | | Ovine | 1500 µg/kg<br>2000 µg/kg<br>1500 µg/kg<br>5000 µg/kg<br>45 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney<br>Milk | |

#### *Withdrawal Periods*

The withdrawal periods are the same as those approved for the reference product:

Cattle: meat and offal: 77 days
Sheep: meat and offal: 107 days

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption. 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.

The withdrawal periods are considered adequate to ensure the safety of consumers of products derived from animals administered the product.

## IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The reference product cited by the applicant was Flukiver 50 mg/ml Solution for Injection, marketed by Eli Lilly & Company Limited, Elanco Animal Health. The efficacy claims for this product are equivalent to those of the reference product.

### *IV.A Pre-Clinical Studies*

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

No tolerance study using the candidate formulation was provided. However, given

- the known toxicological profile of the active substance in the target species,
- that the intended route of administration and the proposed posology of the test product are the same as for the reference product,
- that bioequivalence with the reference product Flukiver 50 mg/ml solution for injection is accepted, and
- that all excipients included in the formulation are the same as in the reference product,

the absence of a specific target animal safety study specific to the test product was accepted.

It was concluded that the target animal safety profile of the test product will be the same as that of the reference product.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

#### *Resistance*

This is an application for a generic veterinary medicinal product submitted in accordance with Article 13(1) of Directive
2001/82/EC, as amended and bioequivalence with a reference product has been demonstrated. It could therefore be concluded that the potential for resistance development will not differ between generic and reference products.

Adequate warnings and precautions appear on the product literature.

### *IV.B Clinical Studies*

Given that bioequivalence between the candidate formulation and the reference product has been satisfactorily demonstrated, laboratory trial and field trial data were not required.

## 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.

***Safety/Efficacy Changes***

| **Summary of change (Application number)** | **Approval date** |
|---|---|
| Change in the meat and offal withdrawal period for sheep (IE/V/0377/001/IA/001) | 22 July 2019 |