IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Chanimec 0.8 mg/ml Oral Solution for Sheep

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number<?xml:namespace prefix = "o" ns = "urn:schemas-microsoftcom:office:office" />	IE/V/0250/001/MR
Name, strength and pharmaceutical form	Chanimec* 0.8mg/ml Oral Solution for Sheep
Active substance(s)	Ivermectin
Marketing Authorisation Holder	Chanelle Pharmaceuticals Manufacturing Ltd. Loughrea Co. Galway Ireland
Legal basis of application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of Authorisation	24th July 2009
Target species	Sheep
Indication for use	For the treatment of gastrointestinal roundworms (adult and fourth larval stage), lungworms (adult and fourth larval stage) and arthropods
ATCvet code	QP54AA01
<CONCERNED Member States>	UK

*Note the MRP was completed with the product name 'Chanectin 0.8 mg/ml Oral Solution for Sheep'. The applicant subsequently changed the name in RMS and CMS to 'Chanimec 0.8 mg/ml Oral Solution for Sheep'.

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 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 ivermectin (0.8 mg/ml) and excipients butylhydroxyanisole, propyl gallate, propylene glycol, disodium edetate, polysorbate 80, disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate monohydrate, benzyl alcohol and purified water The container/closure system consists of:

(i) White flat-bottomed flexi packs (1L, 2.5L, 5L & 6L (5L+1L) composed of high density polyethylene containers, with a tamper evident polypropylene cap.

(ii) Standard containers (jerri-cans) (1L, 2.5L, 5L & 10L) composed of high density polyethylene containers, with a tamper evident polyethylene cap.

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 on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is ivermectin 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 have 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 have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance have 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 have 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)

III.A Safety Testing<?xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />

Pharmacological Studies

Chanimec 0.8 mg/ml Oral Solution has been formulated to have the same qualitative and quantitative composition, in terms of active substances, as the authorised reference product, Oramec Drench for Sheep (VPA 10857/018/001). The Applicant conducted a single in vivo study for investigation of bioequivalence between the test product and an authorised reference product, Oramec Drench. Given that bioequivalence could not be demonstrated through bioavailability studies, the present application has been submitted in accordance with Article 13(3) of the Directive, as amended (so called 'hybrid' application) and safety and efficacy are further supported by proprietary data and published literature.

Based on the findings of comparative pharmacokinetic study, it is accepted that the pharmacokinetic profiles following administration of the test and reference products are broadly similar and that while it is not possible to conclude on bioequivalence for the parameter AUC, the 90% confidence intervals for the parameter C_{max} fell within the prespecified limits. Further, it is noted that the mean half-life of elimination was similar for both test and reference product.

Toxicological Studies

Studies relating to the toxicological effects of ivermectin are published extensively in the literature. The applicant has evaluated a number of these and presented a summary of the information.

It is accepted that the toxicological profile of ivermectin is well known. For further information on the toxicological profile of ivermectin, the reader is referred to the summary toxicological information presented in the EMEA/CVMP MRL Summary Report for ivermectin.

Other Studies

No specific studies were provided concerning potential immunotoxicity. The results of laboratory animals studies and clinical use in humans gave no indications of any effect on the immune system.

Observations in Humans

Ivermectin is widely used in humans for treatment of onchocerciasis and other parasitic diseases at single or repeated doses of 0.15 to 800 mg/kg bw. Tolerance to the compound has been assessed in healthy volunteers and in patients; adverse effects are usually mild and transient. In particular, no effects on the central nervous system were observed. The main effects noted in field and community based trials have been those arising from the death of the parasites, the so-called Mazzotti reaction.

Microbiological Studies

No data on the effects of ivermectin on the human gut flora or micro-organisms used in food processing were available. However, such data were not considered necessary for this class of compound.

User Safety

The formulation was developed based on the reference product 'Oramec Drench for Sheep 0.08% w/v'. The active substance ivermectin is present in both the test product and the reference product at the same concentration. Standard excipients and preservatives are used in the remainder of the formulation of the test product. The selection of excipients and the levels used was based on the applicant's expertise with oral solution formulations. Each of the excipients chosen for the formulation is commonly used in oral solution formulations and is incorporated in the formulation at pharmaceutically acceptable concentrations.

Based on the user safety assessment conducted, it is accepted that the risk to the user is low and will not be greater than that for other similar ivermectin containing products where the concentration of the active ingredient and usage regimen is the same as for Chanimec 0.8 mg/ml Oral Solution for Sheep.

The following user safety statements are proposed:
Wash hands after use.
Do not eat, drink or smoke while handling the product.
Wear impervious gloves when handling or administering the product.
As absorption through the skin can occur, in the event of accidental skin contact, wash the affected area immediately with soap and water.
If accidental eye exposure occurs, flush the eyes immediately with water.

It is accepted that adherence to the proposed user warnings will minimise the potential for any adverse effects.

Envirnomental Risk Assessment

The Applicant has conducted a detailed ERA for the product Chanimec 0.8 mg/ml Oral Solution. Based on the data provided, it is accepted that the use of this product is unlikely to represent an unacceptable risk to the environment when used in accordance with the recommended posology.

III.B Residues documentation

Residue Studies

A confirmatory residue study, conducted to GLP, was provided. The animals included in the study were considered representative of the target population. Further, the numbers of animals included (five animals were slaughtered at each of four evenly distributed time points) was considered appropriate for the determination of a withdrawal period. The product (final formulation) was administered in accordance with the proposed posology.

Following administration of the test item to sheep, ivermectin residue concentrations above the MRL's were not detected in any liver, kidney or fat sample harvested at Day 7 or thereafter.

MRLs

Ivermectin is included in Annex I of Council Regulation (EEC) No 2377/90, with the following MRL for food producing species;

Fat: 100 microgram/kg
Liver: 100 microgram/kg
Kidney: 30 microgram/kg

The marker reside is 22,23-dihydroavermectin.

Withdrawal Periods

Statistical analysis of the results of the residue depletion study is not appropriate given the number of time points at which residue levels are below the limit of quantification. Therefore the 'alternative method', as detailed in the EMEA guide to harmonisation of withdrawal periods, is utilised for the setting of a suitable meat withdrawal period.

The results of the study show that for fat, liver and kidney, the concentrations of ivermectin were below the MRL at Day 7 and at all time points thereafter. Given that Day 7 (first slaughter time point) is the first time point at which residues were detected below the MRL, it is appropriate that a safety factor in the range 10-30 % is applied. Applying a safety factor of 30% results in a withdrawal period of 10 days when rounded up.

A withdrawal period of 10 days is considered adequate to ensure consumer safety.

IV CLINICAL ASSESSMENT (EFFICACY)

Chanimec 0.8 mg/ml Oral Solution has been formulated to have the same qualitative and quantitative composition, in terms of active substances, as the authorised reference product, Oramec Drench for Sheep (VPA 10857/018/001). The Applicant conducted a single in vivo study for investigation of bioequivalence between the test product and an authorised reference product, Oramec Drench. Based on the findings of this study, it is accepted that the pharmacokinetic profiles following administration of the test and reference products are broadly similar and that, while it is not possible to conclude on bioequivalence for the parameter AUC, the 90% confidence intervals for the parameter Cmax fell within the pre-specified limits of 70-143%. When the AUC data are considered, it is evident that systemic availability of ivermectin is greater following administration of the test product compared to the reference product: mean (range) AUC was 687.2 (221.6 – 1314.3) ng/ml/day and 459.3 (191.8 – 1004.0) ng/ml/day for the test and reference products, respectively. Given that, based on these findings, ivermectin has been shown to be more available systemically following administration of the test product, it may be concluded that the test product will be as effective (at least) as the reference product when administered orally to sheep at a dose of 0.2 mg ivermectin/kg. Consequently, the following indication, which is in line with the authorized indication for the reference product (Oramec Drench for Sheep) in the RMS, can be accepted:

For the treatment of mixed infections with the following parasites:
Gastrointestinal roundworms (adult and fourth larval stage)
Haemonchus contortus
Ostertagia circumcincta
Trichostrongylus spp.
Cooperia spp.
Nematodirus spp.
Including *N. battus*
Strongyloides papillosus
Chabertia ovina

(including benzimidazole-resistant strains of *Haemonchus contortus*, *Ostertagia circumcincta* and levamisoleresistant strains of *H. contortus, O. circumcincta* and *T. colubriformis*)

Lungworms (adult and fourth larval stage)
Dictyocaulus filaria

Nasal bot (all larval stages)
Oestrus ovis

Efficacy for the proposed indication, when the product is administered orally to sheep at a dose of 0.2 mg ivermectin/kg, is further supported by information in the published literature.

Based on data provided in respect of target animal tolerance, it can be accepted that the product, when used in accordance with label directions, will not represent an unacceptable risk to the target species.

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 risk/ benefit 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.

None.