IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Flukiver Combi 50 mg/ml + 75 mg/ml oral suspension

PRODUCT SUMMARY

EU Procedure number	IE/V/0222/001/DC
Name, strength and pharmaceutical form	Flukiver Combi 50 mg/ml + 75 mg/ml oral suspension.
Active substance(s)	Closantel (as closantel sodium dihydrate) Mebendazole
Applicant	Elanco GmbH Heinz-Lohmann-Str.4 27472 Cuxhaven Germany
Legal basis of application	Generic application in accordance with Article 13.1 of Directive 2001/82/EC as amended
Date of Authorisation	25 September 2009
Target species	Sheep and lambs
Indication for use	For the treatment and control of liver fluke, gastro-intestinal nematodes, lungworms, cestodes andlarval stages of some arthropods.
ATC Vetcode	QP52AC30
Concerned member states	AT, BE, DE, EL, HU, IS, NL, NO, RO

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 closantel (as closantel sodium dihydrate) and mebendazole as active substances and the excipients propylene glycol, microcrystalline cellulose and carboxymethylcellulose sodium, sodium lauryl sulphate, hypromellose, simethicone emulsion (30%) USNF and purified water.
The product is packaged in one of the following primary packaging configurations:
1L, 2.5L and 5L flasks:

-Flask: High-density polyethylene (HDPE) – food grade
-Screw cap: HDPE, tamper evident – food grade
- Nozzle: Cap body: HDPE – food grade
Retainer: HDPE – food grade
Valve: silicone elastosil – food grade
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.
The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substances are closantel (as closantel sodium dihydrate) and mebendazole, established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications 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 substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances 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

Pharmacological Studies

Pharmacodynamics

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application and therefore data on pharmacodynamics are not required.

The information proposed for inclusion in section 5.1 of the SPC for the test product reflects the text approved for section 5.1 of the SPC for the reference product. The reference product is Supaverm oral suspension authorised in Ireland (VPA 10545/013/001, Janssen - Cilag Ltd.).

Pharmacokinetics
The applicant claims exemption from the need to conduct bioequivalence studies in line with section 4, bullet point (c) of the Guideline for Conduct of Bioequivalence Studies (EMEA/CVMP/016/00-corr-FINAL). Given that the formulations of Flukiver Combi oral suspension and Supaverm oral suspension are identical in all respects (same quantitative and qualitative composition), it is accepted that the test product can be considered bioequivalent to the reference product, Supaverm oral suspension, without the need for specific bioequivalence studies.

The information proposed for inclusion in section 5.2 of the SPC for the test product reflects the text approved for section 5.2 of the SPC for the reference product. The reference product is Supaverm oral suspension authorised in Ireland (VPA 10545/013/001, Janssen - Cilag Ltd.).

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been accepted, results of toxicological tests are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk to the user is acceptable.
In addition, the application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. As such, it can be assumed that the risk to the user arising from the active substance will not be any greater for the test product, compared to the reference product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that there was a potential environmental risk to dung fauna. In order to address this potential risk a risk mitigation measure is included in the SPC.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues Documentation

Residue Studies

The applicant has conducted residue depletion studies using the final formulation in sheep.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. Statistical analysis of the results was used to set the withdrawal period.

The proposed withdrawal period for the test product for sheep meat and offal (65 days) is in line with the withdrawal period authorised for the reference product and is considered adequate.

MRLs

Mebendazole is listed in Annex I of Council Regulation 2377/90.The marker substance is the sum of mebendazole methyl (5-(1-hydroxy, 1-phenyl) methyl-1H-benzimidazol-2-yl) carbamate and (2-amino-1H-benzimidazol-5-yl) phenylmethanone, expressed as mebendazole equivalents.
MRLs are listed below:

	Sheep
Muscle	60 microgram/kg
Liver	400 microgram/kg
Kidney	60 microgram/kg
Fat	60 microgram/kg

Closantel is listed in Annex I of Council Regulation 2377/90.The marker substance is closantel.
MRLs are listed below:

	Sheep
Muscle	1500 microgram/kg
Liver	1500 microgram/kg
Kidney	5000 microgram/kg
Fat	2000 microgram/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 65 days for meat in sheep are justified.

The product should not be administered to animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology
See safety testing

Tolerance in the Target Species of Animals
A target animal safety study specific to the test product has not been presented with the application. Given that:
· the product is an oral dose form,
· bioequivalence with an authorised reference product is claimed,
· the toxicological profile of the active substance is well know, and
· the excipients are recognised as being safe,
the absence of tolerance studies specific to the test product can be accepted.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. As such, the resistance profile is expected to be the same as for the reference product.
The warnings and precautions that appear on the product literature are in line with the prudent use statements recommended by CVMP for anthelmintics (EMEA/CVMP/EWP/170208/2005).

IV.B Clinical Studies

The applicant claims exemption from the need to conduct bioequivalence studies in line with section 4, bullet point (c) of the Guideline for Conduct of Bioequivalence Studies (EMEA/CVMP/016/00-corr-FINAL). Given that the formulations of Flukiver Combi oral suspension and Supaverm oral suspension are identical in all respects (same quantitative and qualitative composition), it is accepted that the test product can be considered bioequivalent to the reference product, Supaverm oral suspension, without the need for specific bioequivalence studies.
As the test product is accepted to be bioequivalent to Supaverm oral suspension, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.
The proposed SPC text reflects the authorised SPC of the reference product.

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.
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.