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PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

FLUDOSOL 200 mg/mL
Suspension for use in drinking water for pigs and chickens

PRODUCT SUMMARY

EU procedure number	FR/V/0449/001/DC
Name, strength and pharmaceutical form	FLUDOSOL 200 mg/mL suspension for use in drinking water for pigs and chickens
Applicant	DOPHARMA RESEARCH ZALMWEG 24 4941 VX RAAMSDONKSVEER NETHERLANDS
Active substance(s)	Flubendazole
ATC vetcode	QP52AC12
Target species	Pig and chicken
Indication for use	For oral use. The product must be diluted in drinking water before administration.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended
Date of completion of the original decentralised procedure	08/02/2023
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, HR, HU, IE, IT, LT, LV, LU, NL, NO, PL, PT, RO, SE, SK

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the potential adverse reactions are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains the active substance flubendazole at a concentration of 200 mg/mL and the following excipients : methyl parahydroxybenzoate, propyl parahydroxybenzoate, adipic acid, polysorbate 80, simethicone emulsion, propylene glycol and water purified.

The containers and closure systems are described in the SPC.

The choice of the formulation and the presence of preservative are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The VMP will be manufactured in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Validation data on the VMP have been presented for pilot batches and process validation for full-scale batches will be performed post-authorisation.

C. Production and control of starting materials

The active substance is Flubendazole, an established active substance described in the European Pharmacopeia. 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.

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 VMP.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for pilot scale batches have been provided demonstrating compliance with the specification.

F. Stability tests

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 VMP throughout its shelf life when stored under the approved conditions.

3. SAFETY DOCUMENTATION (safety and residues tests)

This is a hybrid application according to Article 13(3) of Directive 2001/82/EC as amended by 2004/28/EC, which is similar to a reference product and rely in part on the results of the appropriate safety and residue studies for this reference product, and in part on new data.

Warnings and precautions as listed on the product literature are mostly the same as those of the reference VMP and are adequate to ensure safety of the product to users, the environment and the consumers.

A. Safety tests

Pharmacological studies

No studies were provided in support of this hybrid application. See part IV.

Toxicological studies

This application is submitted as a generic hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended by 2004/28/EC.

The toxicological profile of flubendazole was assessed by the CVMP during the MRL procedure, therefore, no further data about the toxicological profile of the active substance is required.

User safety

The applicant has prepared a User Safety Risk Assessment broadly in accordance with guideline EMEA/CVMP/543/03-FINAL. However, the applicant has been asked to update the RMMs to take into account the outcome of the URA and to be in line with similar authorized veterinary medicinal products.

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

Environmental Risk Assessment

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentration in soil is less than 100 µg/kg.

B. Residues documentation

Residue tests

The applicant has conducted 4 depletion studies.
- one study in pig after administration of the product at 1 mg of flubendazole/kg/day for 5 days.
- one study in pig after administration of the product at 2.5 mg of flubendazole/kg/day for 2 days.
- one study in broilers after administration of the product at 1.43 mg of flubendazole/kg/day for 7 days.
- one egg depletion study in laying hens after administration of the product at 1.43 mg of flubendazole/kg/day for 7 days.

Maximum Residue Limits

The active substance is included in table 1 of the annex of the Commission Regulation (EU) No. 37/2010, as follows,

FLUBENDAZOLE						
Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**
Sum of flubendazole and (2-amino 1H-benzimidazol-5-yl) (4fluorophenyl) methanone	Poultry, porcine	50 µg/kg 50 µg/kg 400 µg/kg 300 µg/kg	Muscle Skin + fat Liver Kidney	No entry	Antiparasitic agents/ Agents against endoparasites	37/2010 of 22.12.2009
flubendazole	Poultry	400 µg/kg	Eggs			

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:

Meat and offal:
Pigs: Meat and offal: 4 days.
Chickens: Meat and offal: 2 days.
Eggs: Zero days.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

This is a hybrid application according to Article 13(3) of Directive 2001/82/EC as amended, which is similar to a reference VMP and rely in part on the results of the appropriate pre-clinical and clinical studies for this reference product, and in part on new data.

A. Pre-Clinical Studies

Pharmacology

No studies were provided in support of this hybrid application.

Development of resistance and related risk in animals

The applicant has conducted a literature search about the mechanisms by which resistance develops and the current level of resistance in target parasites.

Appropriate warnings are inserted in the SPC to advise against practices that may increase risk of resistance.

Dose determination and confirmation

Four dose confirmation studies (one in pigs, three in chickens) were conducted in accordance with the GCP principles (VICH GL 9) and the VICH anthelmintic guidelines (VICH GL 7, 16 and 21).

The results of the dose confirmation study support the efficacy of the veterinary medicinal product against migratory L3 larvae, intestinal L4 larvae and adult stages of *Ascaris suum* in experimentally infected pigs treated at the dose of 2.5 mg flubendazole per kg body weight daily for 2 days.

The results of the dose confirmation studies conducted in naturally infected chickens and treated at the dose of 1.43 mg flubendazole per kg body weight daily for 7 days, support the efficacy of Veterinary medicinal product against the adult stages of *Ascaridia galli*, *Heterakis gallinarum* and *Capillaria* spp.

The following indications can be accepted:

In pigs:
Treatment of helminthiasis caused by *Ascaris suum* (adult, migratory (L3) and intestinal (L4) larval stages).

In chickens:
Treatment of helminthiasis caused by *Ascaridia galli* (adult stages), *Heterakis gallinarum* (adult stages), *Capillaria* spp. (adult stages).

Tolerance in the target species of animals

No tolerance study has been provided. However, it is accepted that the tolerance in the target species of veterinary medicinal product is comparable to that of the reference product.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

B. Clinical trials

No clinical trial is required as this is a hybrid application to Article 13 (3) of Directive 2001/82/EC.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP :

None