IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Fluboral 200 mg/ml, suspension for use in drinking water for pigs and chickens

PRODUCT SUMMARY

EU Procedure number	IE/V/0664/001/DC
Name, strength and pharmaceutical form	Fluboral 200 mg/ml suspension for use in drinking water for pigs and chickens
Active substance(s)	Flubendazole
Applicant	Dechra Regulatory B.V., Handelsweg 25 5531 AE Bladel Netherlands
Legal basis of application	Hybrid application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of procedure	23/11/2022
Target species	Pigs and chickens
Indication for use	Chickens: Treatment of helminthiasis caused by: - *Ascaridia galli* (adult stages) - *Heterakis gallinarum* (adult stages) - *Capillaria* spp. (adult stages) Pigs: Treatment of helminthiasis caused by *Ascaris suum* (adult and L4 intestinal stages)
ATC vet code	QP52AC12
Concerned Member States	AT, BE, DE, DK, ES, FR, HR, IT, PL, PT, NL, SI, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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

This application for Fluboral 200 mg/ml suspension for use in drinking water for pigs and chickens was submitted using the decentralised procedure by Dechra Regulatory B.V., in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC, as amended. The product contains flubendazole as the active substance.
The reference veterinary medicinal product cited is Solubenol®100 mg/g oral emulsion (VPA 10047/040/001, Elanco Animal Health). The reference product has been authorised within the Community for not less than 10 years based upon a full dossier and is accepted as being a suitable reference product.
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. Composition
The products contain 200 mg/ml of flubendazole as the active substance and the excipients methyl parahydroxybenzoate, propyl parahydroxybenzoate, propylene glycol, poloxamer 407, sodium chloride, simethicone emulsion and purified water.
The containers are semi-transparent high density polyethylene bottles closed with white high density polyethylene screw-cap containing low density polyethylene sealing element or semi-transparent high density polyethylene canister closed with white polypropylene screw-cap containing low density polyethylene sealing element.
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 an established active substance described in the European Pharmacopoeia (Ph. Eur). 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.
Ph. Eur. compliant or in-house specifications are provided for all excipients.

D. 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.

E. Control Tests on Intermediate Products
Not applicable.

F. 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.

G. Stability
Stability of the Active Substance
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 of the Finished Product
Stabiity data were supplied for batches tested under VICH conditions. Stabilitiy data is provided to support the in-use shelf life following suspension of the product in drinking water. The product meets all requirements of the proposed shelf-life and in-use shelf life, as specified in the SPC.

H. Genetically Modified Organisms
Not Applicable.

J. Other Information
Not Applicable.

III. SAFETY ASSESSMENT

III.A Safety Testing

Pharmacological Studies

As this is a hybrid application, the applicant has provided bibliographical data which show that flubendazole acts by binding to tubulin of the parasite and inhibiting micro tubular assembly in absorptive cells, leading to decreased absorption and digestion of nutrients. This results in death of the parasite. Furthermore, egg hatching is also inhibited.

The applicant has also provided bibliographical data which show that flubendazole is poorly soluble in aqueous systems, such as the gastrointestinal tract, which results in a low dissolution rate and low absorption. This is reflected by the high faecal excretion of unchanged parent drug. The small fraction absorbed is extensively metabolised by first-pass metabolism in the liver, involving carbamate hydrolysis and ketone reduction. The biotransformation products are conjugated to glucuronides or sulphate conjugates and excreted with the bile and the urine. The excretion with urine is relatively low and consists almost exclusively of metabolites with only small amounts of unchanged compound. In pigs and chickens, the half-life of flubendazole and its metabolites in plasma is 12 hours to 2 days.

Toxicological Studies

The applicant has provided bibliographical data which adequately summarise the toxicity of the active substance, flubendazole. In summary, based on LD_{50} values, it is accepted that the acute toxic potential of flubendazole is low. An oral NOAEL of 2.5 mg/kg/day was established based on a three-month repeat dose toxicity study in dogs. A NOAEL of 10 mg/kg/day was established for reproductive toxicity. There is no evidence of genotoxicity or carcinogenicity.

The excipients are commonly used in oral veterinary pharmaceuticals.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the most likely routes of exposure to the product are dermal, oral and ocular routes.

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

- The veterinary medicinal product can cause skin and eye irritation, and hypersensitivity reactions.
- Direct contact with the product should be avoided. People with known hypersensitivity to flubendazole should avoid contact with the veterinary medicinal product.
- Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.
- Wash hands after use.
- In the event of eye contact, rinse thoroughly with water and if conjunctival redness persists, seek medical advice.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because all $PEC_{soil\ initial}$ values are below the threshold of 100 µg/kg. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies

The applicant has conducted four residue depletion studies.

Two residue depletion studies using the final formulation at dose rates of 1 mg flubendazole/kg bodyweight for 5 days, and 2.5 mg flubendazole/kg bodyweight for 2 days respectively, were conducted in finishing pigs in accordance with GLP and the relevant guideline. Samples of tissues were taken from animals at several time points.

One residue depletion study was conducted in broiler chickens using the final formulation at a dose rate of 1.43 mg flubendazole/kg bodyweight for seven consecutive days, in accordance with GLP and the relevant guideline. Samples of tissues were taken from animals at several time points.

One residue depletion study was conducted in laying hens using the final formulation at a dose rate of 1.43 mg/kg bodyweight for seven consecutive days, in accordance with GLP and the relevant guideline. Eggs were collected at several time points, for an appropriate duration.

The analytical method was LC-MS/MS. The method was fully validated in all matrices.

MRLs

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

	Pigs	**Chickens**
Muscle*	50 µg/kg	50 µg/kg
Liver*	400 µg/kg	400 µg/kg

Kidney*	300 µg/kg	300 µg/kg
Fat / skin*	50 µg/kg	50 µg/kg
Eggs**		400 µg/kg

* Sum of flubendazole and (2-amino-1H-benzimidazol-5-yl)(4flourophenyl)methanone
** Flubendazole

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

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Pigs:
Meat and offal:
1mg/kg for 5 days: 4 days
2.5mg/kg for 2 days: 5 days

-
Chickens:
Meat and offal: 2 days
Eggs: zero days

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies
Pharmacology
Please refer to Part III.

Tolerance in the Target Species of Animal
Bibliographical data have been provided which show that flubendazole is well-tolerated in the target animal species pigs and chickens when administered at the recommended treatment dose. This conclusion is supported by observations made during the residue and dose confirmation studies conducted with the product.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
The bibliographic information provided suggests that there are no recently published reports in the literature of reduced susceptibility to flubendazole in any of the indicated parasite species in the EU.
Adequate warnings and precautions to mitigate against the development of resistance appear on the product literature.

IV.B Clinical Studies
Laboratory Trials
The applicant has conducted 10 dose confirmation studies, 8 of which were in accordance with GCP.
Four dose confirmation studies (three pivotal using induced infections with recent field isolates; one supportive using natural infection) were conducted in pigs, which demonstrate efficacy against adult and larval (L4 stage) *Ascaris suum* at the dose rate of 1 mg/kg for 5 consecutive days, and against adult *Ascaris suum* at the dose rate of 2.5 mg/kg for 2 consecutive days.
Six dose confirmation studies (three pivotal and three supportive) using naturally infected animals (with the exception of one study in which infection was induced), were conducted in chickens. The pivotal studies provided demonstrate efficacy against *Ascaridia galli (*adult stages), *Heterakis gallinarum* (adult stages) and *Capillaria* spp. (adult stages).

Field Trials
The applicant did not conduct clinical field trials, which is accepted as efficacy against the target parasites has been suitably demonstrated in accordance with the relevant guidance.

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.