FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

FLIMABEND 100 MG/G SUSPENSION FOR USE IN DRINKING WATER FOR CHICKENS AND PIGS

Date:14/02/2013

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0242/001/DC
Name, strength and pharmaceutical form	FLIMABEND 100 mg/g suspension for use in drinking water for chickens and pigs
Applicant	KRKA d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
Active substance(s)	Flubenol
ATC Vetcode	QP52AC12
Target species	Pigs (piglets, pigs for fattening, pregnant sows) and chickens (layer hens, chickens for reproduction, pullets, broilers).
Indication for use	In hens/chickens: Treatment of helminthiasis caused by *Ascaridia galli* (adult stages), *Heterakis gallinarum* (adult stages), *Capillaria* spp. (adult stages). In pigs: Treatment of helminthiasis caused by *Ascaris suum* (adult and intestinal larval stages) in piglets, fattening pigs and pregnant sows.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

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	21/12/2012
Concerned Member States for original procedure	AT, CY, BE, DE, DK, EL, ES, IT, NL, PT, UK

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

II. QUALITY ASPECTS

A. Composition

The product contains flubendazole (100mg/g) and excipients carmellose sodium, xanthan gum, citric acid monohydrate, carbomers, disodium ededate, methylparahydroxybenzoate, propylene glycol, water purified and sodium benzoate.

The container system is a sachet. The particulars of the containers and controls performed are provided and conform to the regulation.

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 from 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 flubendazole, 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.

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 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 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.

An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

SOLUBENOL, 100 mg/g oral emulsion marketed by Janssen-Cilag is the reference product for FLIMABEND 100 mg/g suspension for use in drinking water for chickens and pigs. Both products are used in the same species (pigs and poultry), at the same doses and treatment regimen. Both products are administered via medicated drinking water. They have the same

qualitative and quantitative composition of the active ingredient (flubendazole). The pharmacological aspects of this product are identical to the ones of the reference product.
Pharmacokinetic data for flubendazole orally administered in various food-producing species, including pigs and chickens, are presented in the MRL summary reports (Committee for Veterinary Medicinal Products, 1997; 2006). Flubendazole has a low oral bioavailability in laboratory animals (rats), dogs and target animal species. In all species, more than 50 % of the administered dose was excreted in the faeces as unchanged parent compound. The absorbed (minor) portion is rapidly metabolised and concentrations in the blood and urine are very low. The metabolism involves ketone reduction and hydrolysis of carbamate moiety. Ketoreduction is the major metabolic pathway in chickens, while carbamate hydrolysis predominates in pigs.

Toxicological Studies

SOLUBENOL, 100 mg/g oral emulsion marketed by Janssen-Cilag is the reference product for FLIMABEND 100 mg/g suspension for use in drinking water for chickens and pigs. Both products are used in the same species (pigs and poultry), at the same doses and treatment regimen. Both products are administered via medicated drinking water. They have the same qualitative and quantitative composition of the active ingredient (flubendazole). The toxicological aspects of this product are identical to the ones of the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant has provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

III.B Residues documentation

Residue Studies

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

The analytical methods were fully validated.

MRLs

a. active substances

The active substance is included in table 1 of the MRL regulation 470/2009, 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			

b. excipients

The MRL status of excipients of the product are indicated in the following table:

Excipient	MRL status	ADI
Carmellose sodium	Table 1, no MRL required	-
Xanthan gum	Table 1, no MRL required	-
Citric acid monohydrate	Table 1, no MRL required	-
Carbomers	OUT OF SCOPE	
Disodium edetate	Table 1, no MRL required	-
Methylparahydroxybenzoate (E218)	Table 1, no MRL required	-
Propylene glycol	Table 1, no MRL required	-
Sodium benzoate (E211)	Table 1, no MRL required	-

Withdrawal Periods

The withdrawal periods for the tested product are as follows:

Meat and offal:
Chickens: 2 days
Pigs:

- dose 1 mg/kg body weight for 5 days: 3 days
- dose 2.5 mg/kg body weight for 2 days: 4 days

Eggs: zero days.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

No general tolerance studies in target species have been submitted for the tested product. This has been accepted. Indeed, expected adverse effects at therapeutic dosages and in the

case of overdoses should no be different from those observed with the reference product knowing that:

- Concentration in flubendazole is the same in the tested and the reference product.
- Flubendazole has low oral bioavailability.
- The toxicological profile of flubendazole when administered to pigs and poultry is well known (WHO Food Additives Series 31, CVMP summary report).
- Excipients in the tested product should not raise any toxicological concerns for the target species.
- No adverse effects have been observed in the clinical studies.
- Final formulation of the tested product has been showed to be safe in residue and clinical studies.

Based on the same argumentation, the safety of the product has been considered as demonstrated in laying hens. The product can be administered to these animals.

Laboratory studies in rabbits and rats have not produced any evidence of embryotoxicity, teratogenicity at therapeutic doses. High dosages gave equivocal results. The safety of the product has not been demonstrated in pregnant sows.
In laboratory studies in rats, there were no effects on pups during lactation, but the safety of the product has not been assessed in pregnant and lactating sows.
Consequently, the use of the product during pregnancy and lactation should be subject to a benefit/risk ratio assessment by the responsible veterinarian.

Resistance

Several databases (Veterinary Science, Medline, Embase) were thoroughly searched for publicly available information on resistance of target parasite species (Ascaris suum in pigs, Ascaridia galli, Capillaria spp. and Heterakis gallinarum in chickens), but no reports of resistance were found.

IV.B Clinical Studies

The applicant has performed dose confirmation studies in naturally infected animals in order to establish the clinical equivalence with the reference product.
The efficacy of the product against *Ascaris suum* in pigs was investigated in two studies (adult *A. suum* in the first study and immature *A. suum* in the second one).
The efficacy of the product in chickens was investigated in two studies for *Capillaria spp* and for *Heterakis gallinarum* and in a single one for *Ascaridia galli*.

The five studies were well performed and support the following claims:

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

In pigs:
- Treatment of helminthiasis caused by *Ascaris suum* (adult and intestinal larval stages) in piglets, fattening pigs and pregnant sows.

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.