FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
AGENCE NATIONALE DU MEDICAMENT VETERINAIRE

8 rue Claude Bourgelat –
Parc d'activités de la grande Marche –
Javené – CS 70611 –
35306 FOUGERES

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Coldostin, 4800000 IU/g, powder for use in drinking water/milk

DATE:
01/08/2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0299/001/DC
Name, strength and pharmaceutical form	Coldostin, 4800000 IU/g, powder for use in drinking water/milk
Applicant	DOPHARMA RESEARCH ZALMWEG 24 - 4941 SJ RAAMSDONKSVEER – THE NETHERLANDS
Active substance(s)	Colistin sulfate
ATC Vetcode	QA07AA10
Target species	Cattle (calf), sheep (lamb), pig, chicken and turkey.
Indication for use	Treatment and metaphylaxis of gastrointestinal infections caused by non-invasive Escherichia coli susceptible to colistin. The presence of the disease in the herd should be established before metaphylactic treatment.

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	27/07/2016
Concerned Member States for original procedure	DE, BE, DK, NL, PL, LT, HU, and IT.

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

II. QUALITY ASPECTS

A. Composition

The product contains 4 800 000 IU/g colistine sulfate and lactose monohydrate and Macrogol 400 as excipients.
The packaging of the finished product is as described on the SPC. 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 colistin sulfate, an established substance described in the European Veterinary 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

As this is an hybrid application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to those of the reference product.

The product is bioequivalent to the reference product COLISTINE SULFATE 2 000 000 UI/ML BUVABLE VIRBAC by VIRBAC, which is authorised and marketed in France.

No in-vivo bioequivalence study has been conducted, as:

- The test product is an aqueous oral solution at the time of administration and contains the active substance colistin sulfate in the same concentration as the approved reference product;
- The applicant has demonstrated equivalence between the two products, in terms of dissolutions tests and solubility tests both in water and milk environments

- The excipients do not affect gastrointestinal transit, absorption or in-vivo stability of colistin sulfate;
- The acidity of aqueous oral solutions prepared from both test and reference product is comparable.

Toxicological Studies

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

The toxicological of this product are identical to those 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 provided a phase I and a phase II environmental risk assessment in compliance with the relevant guideline. The assessment concluded that colistin is a very persistent molecule in soils.

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

No residue depletion studies were conducted.

MRLs

a. Active substance

The active substance, colistin, is listed in table I of the MRL Regulation 470/2009.

MRLs are listed below:

Marker residue	*Animal species*	*MRL*	*Target tissues*	*Other provisions*	*Therapeutic classification*
Colistin	All food producing species	150 µg/kg 150 µg/kg 150 µg/kg 200 µg/kg 50 µg/kg 300 µg/kg	Muscle Fat Liver Kidney Milk Eggs	For fin fish the muscle MRL relates to « muscle and skin in natural proportions ». MRLs for fat, liver and kidney do not apply for fish. For porcine and poultry, the fat MRL relates to “skin and fat in natural proportions”.	Anti-infectious agents/Antibiotics

b. Excipients

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

Excipient	MRL status
Macrogol 400	Table1, No MRL required
Lactose monohydrate	Out of scope

Withdrawal Periods

The withdrawal periods agreed for the reference product can be applied to the new product, as follows:

Species	Tissues	**Withdrawal periods**
Bovine, ovine	Meat & offal	1 day
	Milk	Not authorised for use in animals producing milk for human consumption
Chicken	Meat & offal	1 day
	Eggs	Zero days
Pig, Turkey	Meat and offal	1 day

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As this is an hybrid application according to Article 13, and bioequivalence with a reference product has been demonstrated, tolerance data are not required. The excipients of the tested product are safe and extensively used in veterinary medicine.

Resistance

An overview of the level of resistance to colistin in target pathogens and commensal bacteria based on recent bibliographical has been provided to address bacterial resistance to colistin.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

As this is an hybrid application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those 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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment are acceptable.