ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Coliplus 2,000,000 IU/ml Concentrate for Oral Solution for use in drinking water for Cattle, Sheep, Pigs and Chickens

ES: Colistina Divasa 2,000,000 IU/ml Concentrate for Oral Solution for use in drinking water for Cattle, Sheep, Pigs and Chickens

PuAR correct as of 16/11/2018 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0313/001/DC
Name, strength and pharmaceutical form	Coliplus 2,000,000 IU/ml Concentrate for Oral Solution for use in drinking water for Cattle, Sheep, Pigs and Chickens ES: Colistina Divasa 2,000,000 IU/ml Concentrate for Oral Solution for use in drinking water for Cattle, Sheep, Pigs and Chickens
Applicant	DIVASA - FARMAVIC, S.A. Ctra. Sant Hipòlit, km 71 08503 GURB – VIC Barcelona (Spain)
Active substance(s)	Colistin (as colistin sulphate)
ATC Vetcode	QA07AA10
Target species	Cattle (calves), sheep (lambs), pigs and chickens
Indication for use	Treatment of gastrointestinal infections caused by non-invasive *Escherichia coli* susceptible to colistin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	In accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original decentralised procedure	29 April 2009
Concerned Member States for original procedure	Belgium Bulgaria Denmark Germany Greece Hungary Italy Lithuania The Netherlands Poland Portugal Romania Slovakia Spain

I. SCIENTIFIC OVERVIEW

Coliplus 2,000,000 IU/ml Concentrate for Oral Solution for use in drinking water for Cattle, Sheep, Pigs and Chickens is authorised for use in cattle (calves), sheep (lambs), pig and chickens for the treatment of gastrointestinal infections caused by non-invasive *Escherichia coli* susceptible to colistin. The product is intended for use in drinking water and contains 2 MIU[1]/ml of colistin as colistin sulphate (equivalent to 83.33 mg). The product is supplied in white HDPE[2] container with tamper-evident aluminium seal and HDPE screw cap, in 250 ml, 1 litre and 5 litre sizes. The recommended dose for calves, lambs and pigs is 100 000 IU[3] of colistin per kilogram bodyweight daily for 3-5 consecutive days. For poultry the recommended dose is 75 000 IU of colistin per kilogram bodyweight daily for 3-5 consecutive days.

The application was generic made in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The European reference product is Colistine Sulfate 2MUI/ml, Buvable (Virbac SA).

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[4]. 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 product contains the active substance colistin (as colistin sulphate) and excipients benzyl alcohol, EDTA disodium salt and purified water.

The product is presented in white HDPE container with tamper-evident seal and HDPE screw cap in volumes of 250 ml, 1 litre and 5 litres.

The choice of formulation is justified.

[1] Million International Unit
[2] High Density Polyethylene
[3] International Unit
[4] Summary of Product Characteristics

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, colistin sulphate, is monographed in the European Pharmacopoeia (Ph. Eur.) and conforms to a satisfactory Certificate of Suitability (CEP).

The excipients benzyl alcohol, EDTA disodium salt and purified water are monographed in the Ph. Eur. Certificates of analysis were provided for all excipients, and the applicant routinely carries out prescribed tests, adhering to specifications in the monograph.

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

There are no intermediate products.

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.

G. Stability

Active substance:
Data have been provided which indicate that the active substance is stable when stored in the appropriate container under appropriate conditions. The retest period of two years is justified.

Finished product:
Data have been provided which indicate that the finished product is stable for 2 years when stored at a temperature below 25°C.

Results of stability studies established an in-use shelf of 60 days after opening the immediate packaging and 24 hours after dilution or reconstitution according to directions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage

- Store below 25°C

Shelf life

- Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
- Shelf-life after first opening the immediate packaging: 60 days
- Shelf-life after dilution or reconstitution according to directions: 24 hours after dilution in water.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The application was submitted in accordance with Article 13 (i) of Directive 2001/82/EC, as amended by Directive 2004/28/EC, and as such results of safety, preclinical and clinical tests are not required.

Toxicological Studies

The application was submitted in accordance with Article 13 (i) of Directive 2001/82/EC, as amended by Directive 2004/28/EC, and as such results of safety, preclinical and clinical tests are not required.

User Safety

The following precautions are listed on the SPC and product literature:

- People with known hypersensitivity to polymyxins should avoid contact with the veterinary medicinal product.
- It is recommended to wear gloves when handling or administering the product.
- Do not eat, drink or smoke while handling the product.
- In case of accidental eye exposure, wash with plenty of water and seek medical advice immediately and show the label to the physician.
- Wash hands after use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline. The PNEC[5] values derived from several studies were acceptable and in accordance with VICH guidelines. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[5] Predicted No Effect Concentration

III.B Residues documentation

Residue Studies

The application was submitted in accordance with Article 13 (i) of Directive 2001/82/EC, as amended by Directive 2004/28/EC, and as such results of safety, preclinical and clinical tests are not required.

MRLs

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Annex
Colistin	Colistin	All food producing species	150	Fat	Annex I
			150	Muscle	
			150	Liver	
			200	Kidney	
			50	Milk	
			300	Eggs	
Benzyl alcohol					Annex II
EDTA Disodium salt					Annex II
Purified water					Out of scope

Withdrawal Periods

Based on the information provided, the following withdrawal period is acceptable:

Meat and offal: Calves, Lambs, Pig and Poultry: 1 day
Eggs: Zero days
Not permitted for use in animals producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application, there was no requirement to provide pre-clinical or clinical data.

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application, there was no requirement to provide pre-clinical or clinical data.

Tolerance in the Target Species of Animals

As this is a generic application, there was no requirement to provide tolerance data. Data on the target species safety and efficacy were requested with regard to a pre-existing European Reference Product. The PSUR[6] data for October 2001 to October 2006 for the reference product was provided which indicated no issues for target species safety. No comprehensive target species tolerance has been reviewed nationally. As a result of a referral to CVMP[7] of colistin-containing products, a decision was made that the recommended dose rate of colistin in this type of product is safe to the target species.

Resistance

As this is a generic application, there was no requirement to provide data on resistance. However, due to increasing resistance of bacteria for many antimicrobials, the applicant submitted a literature review covering a wide period from 1979 to 2006. The data covered many regions in Europe and across the world. The consensus of the data indicated that resistance of Salmonella species and *E.coli* isolates from various diseased animal submissions or slaughter houses is very low. There does not appear to be a trend of increase over time. Cross resistance with other antibiotics has not been identified, however cross resistance with other polymyxins does occur. The applicant submitted data which covered poultry and pigs mainly, but there was some data indicating the same points for cattle and sheep. This is considered acceptable.

[6] Periodic Safety Update Report
[7] The Committee for Medicinal Products for Veterinary Use

IV.B Clinical Studies

Efficacy and target species safety are considered satisfactory based on the fact that this is a generic product of a ERP[8], the generic product and ERP are the same and that the indication, dose rate and tolerance have been considered acceptable by the CVMP and by the Commision following an Article 35 referral. The indication for the treatment of gastrointestinal infections caused by non-invasive *Escherichia coli* susceptible to colistin and the dose of 100 000 IU of colistin per kilogram body weight daily for 3-5 consecutive days for calves, lambs and pigs, and 75 000 IU of colistin per kilogram body weight daily for 3-5 consecutive days for poultry are considered appropriate.

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.

[8] European Reference Product

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)