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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT

GIRAXA
50 mg/g powder for oral solution

Colistin sulphate

Procedure number: CZ/V/0103/001/DC

MAH: KRKA, d.d., Novo Mesto, Slovenia

Date: 28/02/2007

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0103/001/DC
Name, strength and pharmaceutical form	Giraxa 50 mg/g powder for oral solution
Applicant	Krka, d.d., Novo Mesto, Slovenia
Active substance(s)	Colistin Sulphate
ATC Vetcode	QA07A A10
Target species	Calves, piglets, chickens
Indication for use	Treatment of gastro-intestinal infections caused by Gram negative bacteria (particularly *E. coli* and *Salmonella* spp.) in calves, piglets and chickens.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the veterinary Heads of Agencies website:

http://mri.medagencies.org/veterinary/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	The generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	27/02/2008
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	LT, LV, PL, RO, SI

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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, for 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 claims for this product are equivalent to those of the reference product and fulfil 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 50 mg/g Colistin sulphate (equivalent to 1 200 000 IU) and Lactose monohydrate and sucrose as excipients.

The product is packed in two types of containers – PETP/LDPE foil sachets (100g and 1000 g) and Securibox PP containers with LID PE closures (100 g and 1000 g)

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.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is Colistin sulphate, an established active 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.

Scientific data for the active substance were provided using reference to CoS.

Both excipients are described in the European Pharmacopoeia and comply with relevant monographs.

Packaging materials are standard for the veterinary medicinal products and the dosage form. Their quality is also sufficiently demonstrated.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

It is demonstrated the compliance with the guideline EMEA/410/01 Rev. 2 for the medicinal product Giraxa.

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 are not covered by CEPs and thus they are provided by the Applicant in accordance with the European guidelines. The stability and suitability of defined retest periods are demonstrated.

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.

The claims of 18 hours stability after reconstitution in drinking water and 4 months stability after first opening of the container are demonstrated by relevant stability studies.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL) (*for pharmaceuticals only)*

For generics, insert in the relevant sections as appropriate:

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of *in vivo* bioequivalence tests are not required.

The qualitative and quantitative aspects of this product are identical to the reference product.

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

III.A Safety Testing

Pharmacological Studies

Giraxa is a generic of COLIVET powder for solution, the reference product.

Toxicological Studies

Observations in Humans

The application is exempt from the requirements of safety tests as it is submitted in accordance with Article 13(1) of Directive 2001/82/EC as amended by 2004/28/EC.

User Safety

User safety has been addressed adequately. The product literature contains adequate warnings:

People with known hypersensitivity to polymyxins should avoid contact with the veterinary medicinal product.

Wash hands or exposed skin after use with soap and water. If accidental eye exposure occurs, the eyes should be rinsed carefully with water.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that all RQs were above 1. No warnings regarding environmental safety are therefore required.

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

This is a generic application for **GIRAXA® powder for oral solution** in accordance with Article 13(1) of Directive 2001/82/EC as amended by 2004/28/EC.

GIRAXA® powder for oral solution is a generic of COLIVET® plv.sol.ad.us.vet., the reference product. GIRAXA® powder for oral solution is intended for the same target species, at the same doses and treatment regimen.

The applicant has applied the meat withdrawal period 24 hours (1 day), which is different from the reference product (2days). Due this fact the applicant has conducted residue depletion studies of GIRAXA® powder for oral solution 120 000 000 IU/100g in calves, piglets and chickens. Samples of tissues (meat and offal) were taken from animals at several time points. Results show that residues depleted to below the MRL in all examined tissues before the end of the withdrawal period. Alternative approach was used to set the withdrawal period. After considering submitted information regarding residues depletion in examined tissues **withdrawal period 1 day** (meat and offal of chickens, pigs and calves) seems to be acceptable.

The study of colistin residues in eggs was not performed, because the product GIRAXA® powder for oral solution is not intended for use in laying hens producing eggs for human consumption, as also stated in proposed SPC wording of withdrawal period " not permitted for use in laying birds producing eggs for human consumption".

The analytical method was LC/MS method with SRM. The method was fully validated.

MRLs

Colistin is listed in Annex I of Council Regulation 2377/90 (Commission Regulation (EC) No 1181/2002 of 1st July 2002). The marker substance is colistin.

MRLs for colistin are listed below:

	All food producing animals - colistin MRLs [µg/kg]	
Muscle	150 µg/kg	
Liver	150 µg/kg	
Kidney	200 µg/kg	
Fat / skin	150 µg/kg	
Milk	50 µg/kg	

Withdrawal Periods

Based on the data provided above, a withdrawal period of 24 hours (1day) for meat and offals of chickens, pigs and calves are justified. The product is not permitted for use in laying birds producing eggs for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

For generics, insert in the relevant sections as appropriate:

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended on the basis of essential similarity and therefore data on clinical studies are not required. Bioequivalence studies are not necessary, because the product is powder for oral solution, contains the same active substance in the same concentration as reference product and does not contain inactive substances that can significantly affect the absorption of the active substance.
It should be noted that the proposed indications for use and posology for Giraxa are identical as the pioneer product but because marketing authorisation holder of reference veterinary product, Ceva Animal Health, has reported to The Institute for the State Control of Veterinary Biologicals and Medicaments intention to submit variation, which will lead to removing of the prophylaxis. The treatment purpose only is indicated for the product Giraxa.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided adequate data regarding MIC of the active substance – colistin.

Resistance

The information regarding resistance were submitted during the procedure and adequate warnings and precautions appear on the product literature.

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.