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MUTUAL RECOGNITION PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL
PRODUCT**

APSAMIX COLISTINA 40 mg/g
ES/V/0113/001

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0113/001
Name, strength and pharmaceutical form	APSAMIX COLISTINA 40 mg/g Premix for medicated feeding stuff
Applicant	ANDRÉS PINTALUBA S.A. Pol. Ind. Agro-Reus C/ Prudenci Bertrana, nº 5 43206 Reus (Tarragona) SPAIN
Active substance(s)	Colistin (sulphate)
ATC Vetcode	QA07AA10
Target species	Pigs (Piglets and fattening pigs)
Indication for use	Treatment and prevention of colibacillosis and salmonellosis

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on Heads of Medicines Agencies (Veterinary) HMA(v) website (www.HEVRA.org).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	5-07-06
Date product first authorised in the Reference Member State (MRP only)	11-10-2005
Concerned Member States for original procedure	CZ,EL,HU,IT,PL,PT,SK

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 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:

Active substance:

Colistin (sulphate) 4% activity*,

*4% of colistin activity (in sulphate form) is equivalent to 1,200,000 IU of colistin/g of premix, considering that 1 mg of colistin contains 30,000 IU.

Excipients:

Light liquid paraffin

Macrogolglycerol ricinoleate

Almond and hazelnut shell flour

The product is packaged in bags of 25 Kg with a paper valve with the following layers:

1. White calendered kraft paper outer sheet
2. Intermediate kraft paper sheet
3. Inner sheet of kraft paper joined to a neutral coloured low-density polyethylene bag (in contact with the product)

The bottom of the bag is reinforced with a calendered white kraft paper base. The containers are closed first by heat-sealing and then sewn and bordered along the top.

Mock-up of the container is included in the dossier.

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

II.C.1 ACTIVE SUBSTANCES

Colistin sulphate used for the production of APSAMIX COLISTINA 40 mg/g complies with the requirements fixed in the European Pharmacopoeia, 5th Ed., 2005. Additionally, it complies with the requirements of antibiotic potency established previously by the European Pharmacopoeia, 4th Ed., 2002. The quality of the active ingredient is documented via Drug Master File.

II.C.2 OTHER INGREDIENTS

1) Specifications and routine tests

a) Ingredients described in a Pharmacopoeia

Macrogolglycerol ricinoleate and light liquid paraffin comply with the specifications of the European Ph. 5th Ed. The dossier includes the specifications and mentions the routine test carried out by the applicant in each starting material batch. Certificates of analysis are enclosed from both the manufacturer and the applicant.

b) Other ingredients not described in a pharmacopoeia

Almond and hazelnut shell flour quality are described by an internal monograph. Routine test performed by the applicant are mentioned.

Technical documentation on this excipient is enclosed in Part II,. It includes physical and chemical characteristics, and a complete study of the possible amounts of residues according to the national regulation for compounds to be used in animal feedstuffs. The microbiological control of this component is also performed.

II.C.3 PACKAGING MATERIALS

The product is packaged in 25-kg capacity bags comprised of two sheets of kraft paper, one white calendered kraft paper outer layer and an inner bag made of 100-µm thick low-density polyethylene.

The bags are closed by heat-sealing, and then sewing and bordering at the top of the bag.

Quality specifications and description of the test performed on packaging material can be found in the dossier

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

Certificates of BSE/TSE absence are enclosed for the active substance and the rest of the components.

E. Control on intermediate products (pharmaceuticals)

Not applied.

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.

H. Genetically Modified Organisms

The dossier includes certificates of GMO's absence for Colistin Sulphate and Almond and hazelnut shell flour.

Macroglycerol ricinoleate and light liquid paraffin are not affected by this issue.

J. Other Information

The suitability of the product for the proposed use (to be mixed with the feedstuff) has been demonstrated following the guideline EMEA/CVMP/080-95 "Additional Quality Requirements for Products Intended for Incorporation into Animal Feeding Stuffs".

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics:

The study on pharmacodynamics is based, on bibliographic documentation, on the mechanism of action. Colistin is a bactericidal antibiotic whose action does not depend on the bacterial growth phase; it acts against sensitive bacteria both in the germination phase and in the resting phase. Colistin is absorbed in the bacterial cell wall, where it combines with the structures that preserve the cell's osmotic balance (phospholipids and proteins) and thus disorganises them; the result of this action is an alteration of cell permeability, and the cell components, particularly the purines and pyrimidines, escape from the cell protoplasm, causing the lyses of the susceptible bacteria.

The spectrum of action of colistin comprises exclusively gram-negative bacteria, such as: *Escherichia coli*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, *Bordetella*,

Haemophilus, Klebsiella, Enterobacter, Shigella, Salmonella, Yersinia, Pasteurella and Moraxella.

The company conducted an experimental study in order to assess the degree of in vitro sensitivity to colistin of *Escherichia coli* and *Salmonella typhimurium* strain isolated from pigs. From the presented literature review and from the carried out study, it can be concluded that, despite colistin has been widely used for several decades, there is no evidence of an increase in *Escherichia coli* and *Salmonella Spp* resistances to this antibiotic.

Pharmacokinetics:

The company provided published literature which showed that polymyxins are not absorbed orally due to their high molecular weight; its tissue distribution is not significant and it is excreted in faeces.

An evaluation of gastrointestinal behaviour was performed by the company. The results of this study confirm the absence of significant colistin absorption after administration in the feed for 7 days at a real mean dose of 5.5 mg/kg b.w./day.

Toxicological Studies

The company has provided bibliographical data, which show that colistin has a low toxicity. The toxicity of colistin diminishes depending on the route of administration, in descending order: intravenous, intraperitoneal, subcutaneous and oral (due to its poor absorption and low bioavailability). Colistin presents scant chronic toxicity p.o. when administered continuously in species of rodent and non-rodent mammals, and does not impact the main vital functions. Similarly, according to the findings of the studies on colistin, the latter does not present any mutagenic potential; it does not affect the reproductive function and did not give rise to teratogenic effects in laboratory animals following repeat oral administration.

Observations in Humans

Colistin has been used extensively in human medicines for the treatment of different infections, with a low rate of adverse effects.

Microbiological Studies

See Part IV

User Safety

User safety has been addressed adequately. The SPC contains adequate warnings. The product should not be handled by people with hypersensitivity to colistin.

The ingredients of the medicinal product do not produce toxicity at the concentration used during handling. The greatest percentage of the formulation corresponds to the almond and hazelnut shell flour, which are harmless ingredients. Nevertheless, during handling, irritation in the eyes, skin, mucosa and airways may occur; it may be irritant if swallowed. For these cases, the following safety measures are recommended: a dustproof mask (EN140FFP1 standard), gloves and overalls should be worn and contact with the skin and eyes avoided.

Advice has been included regarding accidental skin or eye contact. General warnings, do not smoke, eat or drink while handling the product, have also been agreed.

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

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that there is no need to carry out studies on environmental effects as the PEC_{soil} values are < 100 . No warnings regarding colistin are therefore required.

The SPC contains a standard phrase in section 6.6 as required.

III.B Residues documentation

Residue Studies

Residue depletion study using the final formulation has been conducted in pigs. Samples of tissues were taken from animals at several time points. None of the sample tissues analysed showed colistin residues above the established limit of quantification. The limit of quantification for each target tissue was established as half of the specified MRL.

The analytical method was HPLC-MS. The method was fully validated.

MRLs

European Commission Regulation (EC) No 1181/2002 (O.J. L 172 of 2 of July of 2002) includes Colistin in Annex I of Council Regulation 2377/90. The marker substance is colistin.

For all producing species, the MRLs are listed below:

Target tissue	MRLs
Muscle	150
Liver	150
Kidney	200
Fat / skin	150
Milk	200
Eggs	300

Withdrawal Periods

Based on the data provided above, a withdrawal period of 1 day for meat of porcine is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Antibacterial Activity

From the presented literature review and from the study “degree of in vitro sensitivity to colistin of Escherichia coli and Salmonella typhimurium strain isolated from pigs” carried out by the applicant, it can be concluded that, despite colistin has been widely used for several decades, there is no evidence of an increase in Escherichia coli and Salmonella Spp resistances to this antibiotic.

PK/PD analysis

This analysis consisted of correlating the results obtained from an in vivo pharmacokinetic study and an in vitro pharmacodynamic study (MICs). The PK/PD (AUC/MIC₉₀, T>MIC₉₀ and Cmax/MIC₉₀) quotients were used as indicators of clinical effects.

The T>MIC₉₀ and of AUC/CMI₉₀ parameters suggests that PK/PD index in vivo calculated in the study may be regarded as a relevant indicator for the clinical

efficacy of the APSAMIX COLISTINA 40 mg/g premix when it is administered orally in swine for 7 consecutive days.

Tolerance in the Target Species of Animals

The applicant has performed an experimental study of the general tolerance of COLISTINA 4% medicated premix, in order to assess the possible adverse reactions and determine the safety margin of the product.

This study was performed in accordance with GLP.

The purpose of this study was to analyse the possible adverse reactions of this active substance by studying the performance and the health of the animals after a 14-day medication phase (twice the proposed period of treatment for Colistina 4% Medicated premix) at the proposed initial dose and at twice this dose. The safety margin of the product was determined from the results of this study.

Based on the results obtained from this study, treatment with feeds medicated with colistin up to 240 ppm, corresponding to a dose of 10 mg/kg b.w./day, had no adverse effects on pigs fed ad libitum during the 14 days of administration.

Resistance

*From the presented literature review and from the study provided by the applicant we can conclude that although colistin has been widely used for several decades there is no evidence of an increase in resistance in *E. coli* and *S. typhimurium* to this antibiotic.*

*Bibliographic data on the degree sensitivity to Commensal micro-organisms (*E. coli* and *Enterococcus* spp) and Zoonotic micro-organisms (*Salmonella* spp and *Campylobacter* spp) for the fulfilment of EMEA/CVMP/244/01-FINAL Guideline were also provided. They demonstrated that colistin does not imply a significant risk as for a possible transmission of resistances through these microorganisms.*

IV.B Clinical Studies

Field Trials

*The applicant has conducted a field clinical trial to assess the efficacy of the product in the control and treatment of diarrhoea caused by *Escherichia coli* in pigs at a dose of 6 mg/kg bw during 5-7 days.*

This efficacy study was designed as a controlled, blind and randomized field trial.

The design of the study is considered suitable for the efficacy assessment of the test product at the therapeutic treatment dose. The product intended for marketing was administered by oral route in feed.

The results showed that the rate of animals without diarrhoea at the end of the medicated period was significantly higher in the medicated group than in the control group.

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.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The quality of the active ingredient was documented via Drug Master File.
Two type IA variations were applied to submit new Ph. Eur. Certificate of Suitability for an active substance from a manufacturer currently approved and from a new manufacturer.

Quality changes

Summary of change (Application number)	Section updated in Module 3	Approval date
Submission of a new Ph. Eur. Certificate of Suitability for an active substance or starting material in the manufacturing process of the active substance a) From a manufacturer currently approved. (ES/V/0113/001/IA/001)	II.C.1	29/05/2007
Submission of a new Ph. Eur. Certificate of Suitability for an active substance or starting material in the manufacturing process of the active substance a) From a new manufacturer. (ES/V/0113/001/IA/002)	II.C.1	29/05/2007