



MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL



agencia española de
medicamentos y
productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

NIPOXYME 1000 mg/g ORAL POWDER

CORREO ELECTRÓNICO

mresvet@agamed.es

temporalIP000428.doc

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443



MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0135/001/MR
Name, strength and pharmaceutical form	NIPOXYME 1000 mg/g Oral Powder
Applicant	ANDERSEN, S.A. Avda. la Llana 123 08191 Rubí (Barcelona) Spain
Active substance(s)	Colistin sulphate
ATC Vet code	QA07 AA10
Target species	Swine
Indication for use	Swine: diarrhoeas caused by the susceptible microorganisms: <i>E.coli</i> , <i>Salmonella spp.</i>



MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (<http://www.hma.eu>).



MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 13 a "Well established veterinary use" of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 25/11/2009
Date product first authorised in the Reference Member State (MRP only)	16/02/2009
Concerned Member States for original procedure	BG, HU, IT, LT, PL, PT and RO.

I. SCIENTIFIC OVERVIEW

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

This veterinary medicinal product is an oral powder for administration in drinking water. It does not contain any excipients and therefore, the manufacturing process consists simply in the packaging of the active substance raw material and its labelling under GMP's conditions.

The product is manufactured 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 medicinal product consists in pure colistin sulfate (1000 mg/g) and no excipients are present. The choice of the formulation is justified.

The powder is packaged in fold-up cardboard boxes with an inner lining of aluminium and low-density polyethylene that are closed by thermo-sealing. The particulars of the containers and controls performed are provided and conform to the regulation. Package sizes of 250 g, 500 g and 1 kg have been authorised.

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.

Given the composition of the veterinary medicinal product, manufacture is particularly straightforward. It is manufactured using conventional manufacturing techniques, process validation data on the product have been presented for pilot scale batches and process validation for full-scale batches will be performed post-authorisation.

C. *Control of Starting Materials*

The active substance is colistin sulfate, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Two manufacturers of colistin sulfate have been proposed: Meiji Seika Kaisha Ltd. (Motosu-Gun, Japan) and Meiji Lukang Pharmaceutical Co LTD (Jinning Shandong, People's Republic of China). They both have up to date Certificates of suitability (No. R1-CEP 1998-91-Rev 00 for Meiji Seika Kaisha Ltd. and R0-CEP 2005-166-Rev 00 for Meiji Lukang Pharmaceutical Co. Ltd.)

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 assays and specifications included are most of those of Ph.Eur. monograph for colistin sulfate and additionally assays for appearance of solution, dissolving rate in water, microbiological quality (according to Ph.Eur. 5.1.4) and filling weight per package unit.

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.

A brief description of the assay protocols with references to the relevant Ph.Eur. texts is included.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance from one of the manufacturers have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Colistin sulfate from the other manufacturer is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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 14-days stability of the medicinal product after first opening of the box and of 24-hour stability of medicated water after its preparation are based on experimental stability results obtained according to relevant European Guidelines on in use stability of medicinal products and on veterinary medicines for administration via drinking water.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT

As this is an application according to Article 13a – well established veterinary use – appropriate scientific literature about safety and residues tests was provided.

III.A Safety Testing

Pharmacological Studies

Colistin acts as a cationic surfactant altering the permeability of the bacteria cell membrane by combining with lipoproteins, giving rise to a loss of nutritive elements such as amino acids, inorganic ions, purines and pyrimidines. It produces an alteration in bacterial metabolism and leads to their death. It also acts by reducing the activity of bacterial endotoxins in the tissue liquids.

The applicant has provided bibliographical data which show that Colistin is poorly absorbed after oral administration, and its concentration in plasma is normally undetectable. It is excreted mainly in faeces.

Toxicological Studies

The applicant has provided bibliographical data which show that is not expected that colistin causes toxicity, included genotoxicity and carcinogenicity, at the recommended posology.

Microbiological Studies

The applicant has provided information and appraisal of potential impact that the use of product can suppose for the development of resistances in bacterium of animal origin with importance in the human health, in accordance with the relevant guideline.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk for the professional user is acceptable when the product is used in accordance with label recommendations.

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

Ecotoxicity

The applicant provided a second phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that the use of colistin sulphate in animals according to the therapeutic regimen established is not expected to have a significant impact on the environment.

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

Residue depletion studies using the final formulation have been conducted in swine. Samples of tissues were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period of 1 day.

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

MRLs

Colistin is listed in Annex I of Council Regulation 470/2009. MRLs are listed below:

ANNEXE	Pharmacologically active substances	Marker residue	Animal species	MRLs	Target tissues	Last Regulation	Other provisions	Therapeutic classification
I	Colistin	Colistin	All food producing species	150 µg/kg	Muscle or Muscle and skin in natural proportions	(1181/02)		ANTI-INFECTIOUS AGENTS
I	Colistin	Colistin	All food producing species	150 µg/kg	Fat or Skin+fat in natural proportions	(1181/02)		ANTI-INFECTIOUS AGENTS
I	Colistin	Colistin	All food producing species	150 µg/kg	Liver	(1181/02)		ANTI-INFECTIOUS AGENTS
I	Colistin	Colistin	All food producing species	200 µg/kg	Kidney	(1181/02)		ANTI-INFECTIOUS AGENTS

Withdrawal Periods

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

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is an application according to Article 13a – well established veterinary use – appropriate scientific literature about safety and residues tests was provided.

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology

Colistin acts as a cationic surfactant altering the permeability of the bacteria cell membrane by combining with lipoproteins, giving rise to a loss of nutritive elements such as amino acids, inorganic ions, purines and pyrimidines. It produces an alteration in bacterial metabolism and leads to their death. It also acts by reducing the activity of bacterial endotoxins in the tissue liquids.

The applicant has provided bibliographical data which show that Colistin is poorly absorbed after oral administration, and its concentration in plasma is normally undetectable. It is excreted mainly in faeces.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance studies using multiples of the recommended dose in the target species. In relation to the tolerance documentation, the bibliography and tolerance study are sufficient, also picks up clearly the great experience that the clinical ones have on this type of therapeutic.

Resistance

The considerations on the MIC90 and on the dose given lead us to assume that the treatment with NIPOXYME ORAL POWDER 1000 at the dosage schedule proposed would offer guarantees of efficacy, avoiding the selection of bacterial resistance by the microorganisms evaluated.

IV.B Clinical Studies

Laboratory Trials

The dosage schedule recommended for the NIPOXYME ORAL POWDER 1000 formulation is the administration of a dose of 5 mg/kg of CL in drinking water for 7 days. In the studies in which this dose was evaluated after oral bolus administration and for 3 days, healing indices of 83% (Ref. 45, dose of 4 mg/kg), 100% (Ref. 46, dose of 4 mg/kg) and 100% (Ref. 47, with a dose of 5 mg/kg) were observed. If we extrapolate these results to the prescribed dose of NIPOXYME ORAL POWDER 1000 with seven days of treatment, it may be concluded that it would be effective for the treatment of colibacillosis.

Field Trials

From the clinical standpoint, a study carried out with NIPOXYME 40 (ref. 48) shows that this product (CL premix for feed), given according to the recommended dosage schedule, is effective in the control and treatment of diarrhoeas caused by enteropathogenic *E. coli* in swine. The study was carried out following the VICH GCP standards. The efficacy of NIPOXYME 40, given for 5 days at a dose of 3.5 mg/kg/doy in the feed, was compared to a reference product (COFAMIX® Colistine 200-R) registered in France. For this purpose, two groups of 103 and 102 animals were used for NIPOXYME 40 and COFAMIX, respectively, presenting naturally occurring diarrhoea. The diagnosis and confirmation of the disease was performed by means of microbiological analysis and determination of the enteropathogenic serotype of the strains isolated. The diarrhoeal outbreak was caused by different enteropathogenic strains of *E. coli*. The group treated with NIPOXYME 40 presented 100% efficacy of treatment, while the group treated with COFAMIX presented a 98.78%. Moreover, this study statistically demonstrated non-inferiority in the efficacy of the treatment with NIPOXYME 40 versus treatment with the reference formulation. The final conclusion of this study was that treatment with NIPOXYME 40, at the recommended dosage schedule, is effective against diarrhoea caused by enteropathogenic *E. coli* in swine, and that the efficacy of this treatment is not inferior to that of the other formulation of the same drug registered in France for this specific condition.

If we take into account that the comparisons between the intestinal concentrations of CL obtained after the administration of feed medicated with NIPOXYME 40 and those obtained after the administration of the NIPOXYME ORAL POWDER1000 formulation in drinking water (Figures 1 and 2) are very similar when related to the dose consumed by the animals, the efficacy of both products may be assumed to be similar. Therefore, if the treatment with NIPOXYME 40 proved to be effective against diarrhoeas caused by enteropathogenic *E. coli* at a theoretical dose of 3.5 mg/kg/day for 7 days (Ref. 48), the treatment with NIPOXYME ORAL POWDER1000 at a higher dose (5 mg/kg/day) and for a longer treatment time (7 days) must also be effective against this type of diarrhoeas in swine.

The treatment demand for NIPOXYME ORAL POWDER 1000 in medicated water for seven days, at a dose of 5 mg/kg/day of CL, would offer guaranteed effectiveness, minimising the risk of selection of resistance by Escherichia coli and Salmonella enterica in diarrhoeal processes in swine.



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 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 veterinary Heads of Agencies website (www.hma.eu).

This section 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.

None