College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Metaxol 20/100 mg/ml solution for use in drinking water for pigs and chickens

Metaxol 20/100 mg/ml solution for use in drinking water for pigs and chickens	NL/V/0198/001/DC
Eurovet Animal Health BV	
	Publicly available assessment report

MODULE 1

PRODUCT SUMMARY

Dutch Registration number	117064
EU Procedure number	NL/V/0198/001/DC
Name, strength and pharmaceutical form	Metaxol 20/100 mg/ml solution for use in drinking water for pigs and chickens
Applicant	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands
Active substance(s)	Trimethoprim and sulfamethoxazole
ATC Vetcode	QJ01EW11
Target species	Pigs (fattening pigs) and chickens (broilers)
Indication for use	Fattening pigs: Treatment and metaphylaxis of: - Post-weaning diarrhoea caused by betahaemolytic K88-positive, K99-positive or 987P *Escherichia coli* strains susceptible to trimethoprim-sulfamethoxazole. - Secondary bacterial infections caused by *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Streptococcus spp*. and *Haemophilus parasuis* susceptible to trimethoprim-sulfamethoxazole. Broilers: Treatment and metaphylaxis of: - Colibacillosis caused by *Escherichia coli* susceptible to trimethoprim-sulfamethoxazole. - Coryza caused by *Avibacterium paragallinarum* susceptible to trimethoprimsulfamethoxazole. The presence of the disease in the group/flock must be established before the product is used

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MODULE 2

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

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28th of April 2016
Concerned Member States for original procedure	AT BE CZ DE EE EL ES FR HU IE IT LT PL PT RO SK UK

I. SCIENTIFIC OVERVIEW

Metaxol 20/100 mg/ml solution for use in drinking water for pigs and chickens 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.
Metaxol 20/100 mg/ml solution for use in drinking water for pigs and chickens 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 proposed veterinary medicinal product is a solution for use in drinking water containing

100 mg/ml sulfamethoxazole and 20 mg/ml trimethoprim as active substances, and propylene glycol, purified water and N-methyl pyrrolidone as solvents. Sodium hydroxide is used for pH adjustment.

The solutions are packed in clear1000 ml and 5000 ml HDPE bottles, closed with tamperproof closures (LDPE for the 1000 ml containers and HDPE for the 5000 ml containers). The materials comply with Commission Directive 10/2011.

The products represent an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines.

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B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques. The manufacturing process is a standard manufacturing process. The production process has been validated by production of three full scale batches. Validation reports have been included.

The tests performed during production are described. Adequate in-process specifications are provided.

C. Control of Starting Materials

The active substances are sulfamethoxazole and trimethoprim, established active substances described in the European Pharmacopoeia. The active substance are manufactured in accordance with the principles of good manufacturing practice. Certificates of suitability have been provided.

The quality of the active substances is suitably controlled by the current version of their monograph of the European Pharmacopoeia, only if it is supplemented by the tests mentioned on the CoS.

Batch analytical data demonstrating compliance with the specifications of both active substances have been provided.

The excipients are in conformity with European Pharmacopoeia requirements.

The primary packaging materials comply with Commission Directive 10/2011.

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, 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.

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G. Stability

A re-test period of 60 months for the active substance sulfamethoxazole has been mentioned on the CoS. Stability data on the active substance trimethoprim have been provided in accordance with applicable European guidelines, confirming a retest period of 48 months.

Stability data on the finished products have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout the claimed shelf life of 36 months when stored under the approved conditions.

Additional stability studies justify the claimed 12 months in-use shelf-life of the product after opening and the claimed in-use shelf-life of the medicated drinking water of 24 hours, when stored under the approved conditions.

H. Genetically Modified Organisms

None

J. Other Information

None

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

Warning statements and precautions as listed in the product literature are based on those of the reference product and supplemented with additional statements, based on increased knowledge and the current state of science. This information is considered adequate to ensure safety of the product to users, consumers and the environment.

III.A Safety Testing

User Safety

Being a generic procedure the applicant refers to the reference product for information on this section.

Additionally the applicant has provided a user safety assessment. Combined with increased knowledge and the current state of science, warning statements and precautions have been added to the product literature, ensuring safety to users of the product.

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Ecotoxicity

Phase I

A Phase II ERA is required as the Phase I assessment showed that calculated soil concentrations exceed 100 µg kg^{-1} for both active substances of the product.

Phase II Tier A A Phase II Tier A assessment was conducted.

The applicant provided studies which enabled a risk assessment.
In order to further characterise the risk for the environment, a refinement of predicted exposures was undertaken.

Based upon the data provided in phase II Tier A, Metaxol will present an unacceptable risk for the terrestrial and groundwater compartment and a Tier B assessment was performed.

Phase II Tier B

A Phase II Tier B assessment and higher tier assessment was conducted.

The applicant provided studies which enabled a further risk assessment.
The results of the higher tier assessment indicate that no unacceptable risk for the environment remains after further refinement.

The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

Environmental properties:

Trimethoprim is persistent in soils.

III.B Residues documentation

Residue Studies

As this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated, results of residue depletion studies are not required.

Withdrawal Periods

Based on the above the following withdrawal periods are justified:

Pig: Meat and offal: 8 days.

Chicken: Meat and offal: 5 days.

Not authorised for use in birds producing eggs for human consumption.

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IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic 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.

Resistance

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.