College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Metrovis 100 mg tablets for dogs and cats Metrovis 250 mg tablets for dogs and cats Metrovis 750 mg tablets for dogs

Date: 9 July 2019

MODULE 1

PRODUCT SUMMARY

Dutch Registration number	REG NL 123140, 123141, 123142
EU Procedure number	NL/V/0249/001-003/DC
Name, strength and pharmaceutical form	Metrovis 100 mg tablets for dogs and cats Metrovis 250 mg tablets for dogs and cats Metrovis 750 mg tablets for dogs
Applicant	Livisto Int'l, S.L. Av. Universitat Autònoma 29 08290 Cerdanyola del Vallès Barcelona, Spain
Active substance(s)	Metronidazole
ATC Vetcode	QP51AA01
Target species	100 mg, 250 mg: dogs and cats 750 mg: dogs
Indication for use	Treatment of gastrointestinal tract infections caused by *Giardia* spp. and *Clostridia* spp. (i.e. *C. perfringens* or *C. difficile*). Treatment of infections of the urogenital tract, oral cavity, throat, and skin caused by obligate anaerobic bacteria (e.g. *Clostridia* spp.) susceptible to metronidazole.

MODULE 2

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

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	250 mg: Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended. 100 mg, 750 mg: Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	17 April 2019
Concerned Member States for original procedure	AT, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LV, PL, PT, RO, SI, UK

I. SCIENTIFIC OVERVIEW

Metrovis 100 mg, 250 mg tablets for dogs and cats and Metrovis 750 mg tablets for dogs are produced and controlled using validated methods and tests, which ensure the consistency of the products released on the market.
It has been shown that the products can be safely used in the target species; the slight reactions observed are indicated in the SPC.
Metrovis 100 mg, 250 mg tablets for dogs and cats and Metrovis 750 mg tablets for dogs are safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the products were demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

The quality, safety and efficacy aspects of Metrovis 100 mg, 250 mg tablets for dogs and cats and Metrovis 750 mg tablets for dogs are based on bioequivalence with the Reference product Metrazol REG NL 5757, which was assessed before there was a requirement to have a public assessment report; therefore no details in this section are available.
Warnings statements and precautions are adopted from the reference product. Additional statements have been added, based on increased knowledge and the current state of science. Adverse events, warnings and contraindications are indicated in the SPC.

II. QUALITY ASPECTS

A. QUALITATIVE AND QUANTITATIVE PARTICULARS

The tablets contain 100 mg, 250 mg or 750 mg Metronidazole and the following core excipients:

Hydroxypropylcellulose, Microcrystalline cellulose, Sodium starch glycolate (type A), Beef flavor, Yeast (dried) and Magnesium stearate.
The tablet is cross scored and meant to be broken in halves or quarters.

The tablets are packed in AL-PVC/PE/PVDC blisters, each containing 10 tablets (100 mg, 250 mg) resp. 8 tablets (750 mg).

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

For the generic 250 mg tablet strength bioequivalence with the reference product is established. According to the comparative dissolution profiles, representative for BCS I formulations, a biowaiver can be granted for the hybrid 100 mg and 750 mg tablet strengths.

B. DESCRIPTION OF THE MANUFACTURING METHOD

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. Suitable preapproval validation results on three production scale batches of each tablet strength have been provided.

The tests performed during production are described.

C. CONTROL OF STARTING MATERIALS

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

The CEP procedure has been employed.

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.

The in-house monographs and additional information in regard to the flavouring agents is acceptable. All other excipients are in conformity with the Ph.Eur. requirements.

None of the starting materials used are affected by the Note for Guidance on TSE/BSE.

D. CONTROL TESTS DURING THE MANUFACTURING PROCESS

Not applicable.

E. CONTROL TESTS ON THE FINISHED PRODUCT

The finished product specification controls the relevant parameters for the pharmaceutical form. All tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

The dissolution specifications in accordance with the relevant RP. The QC dissolution method is equal to the USP method that was used with the comparative dissolution studies.

Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. STABILITY

The retest period of 48 months for metronidazole when stored under the approved conditions is stated on the CEP.

Stability data on the finished product have been provided in accordance with applicable VICH guidelines.

According to the 12/18 months stability results provided the claimed shelf life of 2 years can be granted for all tablet strength.
An in-use shelf life of 3 days after first use (divided tablets), without special storage restrictions can be granted.

G. OTHER INFORMATION

None

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application (250 mg) respectively a hybrid application (100 mg, 750 mg) according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological, pharmacological and clinical tests are not required.

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 / consumers. Additional statements have been added, based on increased knowledge and the current state of science. Adverse events, warnings and contraindications are indicated in the SPC.

III.A Safety Testing

User Safety

Being a generic (250 mg) respectively a hybrid (100 mg, 750 mg) procedure the applicant refers to the reference product for information on this section.

Additionally, the applicant has provided a user safety assessment in compliance with the relevant guideline. Combined with increased knowledge and the current state of science, 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 environmental risk assessment can stop in Phase I because this product is intended for use in dogs and cats (100 mg, 250 mg) respectively dogs (750 mg) and a Phase II assessment is not deemed necessary.

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

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application (250 mg) respectively a hybrid application (100 mg, 750 mg) 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.

Tolerance in the Target Species of Animals

Additionally to the above, based on increased knowledge and the current state of science, warning statements and precautions have been added to the product literature ensuring safety to the target animals. Adverse events, warnings and contraindications are indicated in the SPC.

Resistance

As this is a generic application (250 mg) respectively a hybrid application (100 mg, 750 mg) application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological and pharmacological and clinical tests are not required. However, the SPC and Product Literature are updated according to the Revised Guideline on the SPC for Antimicrobial Products (EMEA/CVMP/SAGAM/383441/2005).

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 Heads of Vetrinary Medicines 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.