Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Spizobactin 750,000 IU/125 mg
Spizobactin 1,500,000 IU/250 mg
Spizobactin 3,000,000 IU / 500 mg

Chewable tablets for dogs

Date: 10 October 2017

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0171/001-003/DC
Name, strength and pharmaceutical form	Spizobactin 750,000 IU/125 mg Spizobactin 1,500,000 IU/250 mg Spizobactin 3,000,000 IU/500 mg Chewable tablets for dogs
Applicant	Le Vet Beheer B.V. Wilgenweg 7 NL-3421 TV Oudewater
Active substance(s)	Spiramycin Metronidazole
ATC Vetcode	QJ01RA04
Target species	Dog
Indication for use	For the adjunct treatment of mechanical or surgical periodontal therapy in the treatment of multi-bacterial infections of periodontal and related (peri)oral conditions – e.g. gingivitis, stomatitis, glossitis, periodontitis, tonsillitis, dental fistula and other fistulas wounds in the oral cavity, cheilitis and sinusitis - in dogs caused by microorganisms susceptible to spiramycin / metronidazole, such as Gram-positive bacteria and anaerobes

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Spizobactin 750,000 IU/125 mg Application in accordance with Article 13(1) of Directive 2001/82/EC as amended Spizobactin 1,500,000 IU/250 mg and Spizobactin 3,000,000 IU / 500 mg Application in accordance with Article 13(3) of Directive 2001/82/EC as amended
Date of completion of the original Decentralised procedure	28 June 2017
Date product first authorised in the Reference Member State (MRP only)	N.A:
Concerned Member States for original procedure	AT; BE; BG; CY; CZ; DK; EE; EL; ES; FI; FR; HR; HU; IE; IS; IT; LT; LU; LV; NL; NO; PL; PT; RO; SI; SK; UK

I. SCIENTIFIC OVERVIEW

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 and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The safety and efficacy aspects of this product are identical to Suanatem forte film coated tablets (Merial; MA Nr. 625.00.01). The initial application for Suanatem forte film coated tablets was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 750.000 IE spiramycin / 125 mg metronidazole respectively 1.500.000 IE spiramycin / 250 mg metronidazole respectively 3.000.000 IE spiramycin / 500 mg metronidazole per tablet. The excipients are pregelatinized starch, microcrystalline cellulose, lactose monohydrate, hydroxypropylcellulose, yeast (dried), chicken flavour, silica (colloidal anhydrous), and magnesium stearate.

The container system is an aluminium-PVC/PE/PVDC blister in cardboard boxes containing 1, 2 or 3 blisters of 10 tablets. There are also cardboard boxes containing 10 separate cardboard boxes, each containing 1 blister of 10 tablets.

The choice of the adjuvants in the formulation is well justified.

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 at 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

The active substances spiramycin and metronidazole are established substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

Not applicable.

E. 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.

F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances 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.

The claim of a 3-day stability after broaching is based on the demonstration of stability for two batches broached and stored 3 days at +25ºC/60% RH.

G. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

A GCP-compliant single dose, two-period, two-sequence, crossover *in-vivo* bioequivalence study of Spizobactin-S and Suanatem Forte tablets containing 125 mg metronidazole / 750.000 IU spiramycin after oral administration in Beagle dogs was conducted.

Metronidazole was demonstrated to be bioequivalent for AUC_{last} and for C_{max}, within the acceptance limits of 80-125%.

The acceptance limits of Cmax of Spiramycin-I had been widened prospectively to the range of 70-143%. Clinical justification for widening of the limits was accepted based on pilot data that had shown high variability of spiramycin with intra-subject % CVs for C_{max}, AUC_{0-12h} and AUC_{inf} of 31, 21 and 22%, respectively and because no negative impact on efficacy and safety was expected. Following this justification and the results of the pilot study a higher than standard number of animals was included in the bioequivalence study.

Bioequivalence for C_{max} of spiramycin-I could be demonstrated within the widened acceptance limits while bioequivalence of Spiramycin-I could not be demonstrated for AUC_{last}, although this was missed only narrowly (126%). From a clinical perspective the slight exceedance of the AUC_{last} confidence interval is not expected to be detrimental with regard to efficacy and safety. Thus, the test and the reference product are regarded as bioequivalent.

A dissolution study was conducted according to bioequivalence guideline EMA/CVMP/016/00-Rev.2 and demonstrated similarity of the *in-vitro* dissolution of each strengths of Spitzobactin chewable tablets (containing 125 mg metronidazole / 750.000 IU spiramycin, 250 mg metronidazole / 1.500.000 IU spiramycin, 500 mg metronidazole / 3.000.000 IU spiramycin) at three different pH values.

Toxicological Studies

As this is a generic/hybrid application submitted according to Article 13(1) and Article 13(3) of Directive 2001/82/EC as amended results from toxicological studies are not required. The largest tablet of the veterinary product contains 500 mg metronidazole and 3.000.000 IU spiramycin per tablet. Metronidazole has been classified mutagenic in mammalian cell systems and in vivo in the mouse bone marrow test. Metronidazole is possibly carcinogenic in humans and has been shown to have some teratogenic potential. Spiramycin normally causes very few adverse effects (mainly gastro-intestinal disturbances) but may trigger various hypersensitivity reactions.
The product does not contain any odd excipients, which would require further investigation. The pharmaco- toxicological properties apply to the reference product Suanatem likewise.

User Safety

A comprehensive user risk assessment has been provided including a hazard identification of the active ingredients and excipients. Relevant exposure scenarios have been considered. The applicant has made a useful user risk characterisation and the proposed measures / precautions exceed those that are given for the reference product. Warning phrases and mitigation measures included in the product literature are considered sufficient to ensure safety of the user when the product is administered as indicated.

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Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because the products are only used to treat individual non-food animals.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

IV. CLINICAL ASSESSMENT (EFFICACY)

As these are generic applications according to Article 13(1) and Article 13(3) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are comparable to those of the reference product. The wording of the indications was modified to promote the rational use of the fixed combination antimicrobial product by adding "*For the adjunct treatment of mechanical or surgical periodontal therapy in the treatment of multi-bacterial infections*...". In addition, further warnings on the rational use were included in SPC sections 4.4 and 4.5. Besides, causative target pathogens "… *such as Gram-positive bacteria and anaerobes*" were supplemented.

IV.A Pre-Clinical Studies

Pharmacology

The SPC text of the pharmacodynamic information of the reference product was updated according to requirements of the Revised Guideline on the SPC for Antimicrobial Products (EMA/CVMP/SAGAM/383441/2005).
The SPC text of the pharmacokinetic information was supplemented by pharmacokinetic data of this product generated in the bioequivalence study.

Tolerance in the Target Species of Animals

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography / information provided suggests that there is no potential increase or change in resistance profiles of potential target pathogens in dogs to spiramycin and metronidazol.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Since the application is made on the basis of essentially similarity to a reference product in accordance with Article 13 of Directive 2001/82/EC as amended, data from clinical studies are not required.

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 Veterinary Medicinal 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>

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