Veterinary Medicines Directorate

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MUTUAL RECOGNITION

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Synuclav 50 mg Tablets for Dogs and Cats

PuAR correct as of 14/01/2019 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0197/E001
Name, strength and pharmaceutical form	Synuclav 50 mg Tablets for Dogs and Cats
Applicant	Norbrook Laboratories Limited
Active substances	Amoxicillin, clavulanic acid
ATC Vetcode	QJ01CR02
Target species	Dogs and cats
Indication for use	Treatment of the following infections caused by β-lactamase producing strains of bacteria sensitive to amoxicillin in combination with clavulanic acid: Skin infections (including superficial and deep pyodermas) caused by susceptible *Staphylococci* Urinary tract infection caused by susceptible *Staphylococci* spp. or *Escherichia coli* Respiratory infections caused by susceptible *Staphylococci* Enteritis caused by susceptible *Escherichia coli* It is recommended to carry out suitable tests for sensitivity testing when initiating the treatment. The treatment should only proceed if sensitivity is proven to the combination.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/BC.
Date of completion of the original mutual recognition procedure	25 February 2004
Date product first authorised in the Reference Member State (MRP only)	28 January 2003
Concerned Member States for original procedure	Austria, Belgium, Denmark, France, Italy, The Netherlands, Norway, Portugal, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This application was for the renewal of a mutually recognised product, Synuclav 50 mg Tablets for Dogs and Cats. The product was first authorised in the UK on 28th January 2003 and was approved via Mutual Recognition in Austria, Belgium, Denmark, France, Italy, The Netherlands, Norway, Portugal, Sweden and Spain on 25th February 2004. A joint application for Synuclav 50 mg and 250 mg tablets were originally submitted, and were noted to be based on essential similarity with corresponding strengths of Synulox Palatable Tablets, via the dossier for the identical products, Noroclav Tablets 50 mg and 250 mg. Synuclav 50 mg Tablets for Dogs and Cats is administered at 12.5 mg combined actives mg/kg bodyweight twice daily. The tablets may be crushed and added to food.

The product is for the treatment of infections caused by β-lactamase producing strains of bacteria sensitive to amoxicillin in combination with clavulanic acid. These are skin infections caused by susceptible *Staphylocci* spp., Urinary tract infection caused by susceptible *Staphylococci* spp. or *Escherichia coli,* respiratory infections caused by susceptible *Staphylococci* spp., respiratory infections caused by susceptible *Staphylococci* spp., and enteritis caused by *E. coli.* The product must not be used in known cases of hypersensitivity, and must not be used in guinea pigs, hamsters or gerbils. Serious kidney dysfunction is also a contraindication.

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[1]. The product is safe for the user,

[1] SPC – Summary of Product Characteristics.

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

II. QUALITY ASPECTS

A. Composition

The product contains amoxicillin (as amoxicillin trihydrate) 40 mg, and clavulanic acid (as potassium clavulanate) 10 mg and the excipients are carmosine lake (E122), sodium starch glycolate, copovidone K24-36, magnesium stearate, microcrystalline cellulose, calcium carbonate, heavy magnesium carbonate and roast beef flav-o-lok.

The container/closure system is a high density polyethylene tub with a polyethylene screw cap lid containing 100 or 500 tablets. A sachet of dessicant is included in each container. The product is additionally presented as 2, 10 or 50 (aluminium-aluminium) blister strips containing 10 tablets per strip. 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

The active substances are amoxicillin and clavulanic acid, established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

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.

All excipients, with the exception of carmosine lake and roast beef flavour, are the subject of European Pharmacopoeial monographs. The ingredient specifications comply with the requirements of these monographs. The beef flavour has specifications that have been developed on the basis of tests for appearance, odour and moisture. The supplier certifies that the flavour is in compliance with the requirements for a flavour used in food. The supplier's specification for the colouring agent, carmosine lake has been cited. This

requires compliance with European requirements for food additive E122 and directive 95/45/EC concerning colours for food use.

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

There are no intermediate products.

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 substances and the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The product has a shelf-life as packaged for sale of 2 years for blister packs and 6 months for tubs.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

This application was originally submitted in accordance with Article 13 (1) of Directive 2001/82/EC, and therefore the results of pharmacological, toxicological and clinical trials were not required.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which showed that the most likely route of exposure is via the dermal route. The risk of ingestion of the product is minimal as it is prescribed by a veterinarian, however, suitable warnings are cited in the SPC:-

- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.

- Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.

- Handle this product with great care to avoid exposure, taking all recommended precautions.

- If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

- Wash hands after use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. 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

Not applicable.

IV CLINICAL ASSESSMENT (EFFICACY)

As this was originally a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. Dissolution tests were performed as appropriate for the original application.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Amoxicillin is a beta-lactam antibiotic containing both beta-lactam and thiazolidine rings. Activity is seen against both susceptible Gram-positive and Gram-negative bacteria. The target bacterial cell wall is prevented from forming, causing the lysis of growing cells. Clavulanic acid extends the target species for which beta-lactam is an inhibitor, by blocking the action of beta-lactamase, which inhibits beta-lactam.

Pharmacokinetics

Amoxicillin has good absorption in the target mammal, with a small distribution volume and short terminal half-life, and excretion in the main performed via the kidneys. Clavulanic acid is also well absorbed, has a short half-life and is also excreted mainly via the kidneys.

Tolerance in the Target Species of Animals

The applicant conducted target animal tolerance studies where appropriate.

IV.B Clinical Studies

Bioequivalence was established with the parent product, Synulox Palatable Tablets, and there was therefore no requirement to produce further data for this section with regard to dogs. Studies were provided during a variation procedure to include cats as an additional target species. A GLP[2]-compliant bioequivalence study compared Clavapet 50 mg Tablets for Dogs and Cats with Synulox Palatable Tablets in a study with a suitable number of cats. C_{max}[3], T_{max}[4] and AUC[5] were comparable for both products and the results were with the defined confidence limits, thus bioequivalence was ascertained.

An additional study was performed in which the product was analysed at 1x and 3x the recommended dose. No adverse effects were noted.

[2] GLP – Good Laboratory Practise.
[3] C_{max} – maximum observed plasma concentration of the active substance.
[4] T_{max} – Time at which the maximum plasma concentration of the active substance was observed.
[5] AUC – Area under the time versus concentration curve.

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 benefit/risk 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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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