ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Nisamox Palatable Tablets 500 mg for Dogs

Nisamox Tablets 400mg/100mg for Dogs
(France)

PuAR correct as of 11/01/2019 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0246/001/MR
Name, strength and pharmaceutical form	Nisamox Palatable Tablets 500 mg for Dogs
Applicant	Norbrook Laboratories Ltd. Station Works Camlough Road Newry County Down Northern Ireland
Active substances	Amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate).
ATC Vetcode	QJ01CR02
Target species	Dogs
Indication for use	Treatment of the following infections caused by beta-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 infections caused by susceptible *Staphylococci* 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 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	Mutual Recognition application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	25 July 2007
Date product first authorised in the Reference Member State (MRP only)	06 June 2006
Concerned Member States for original procedure	Belgium France Italy Netherlands Portugal Spain

I. SCIENTIFIC OVERVIEW

This product is a tablet containing amoxicillin and clavulanic acid indicated for broad-spectrum antibacterial therapy in dogs. The nominal combined antibiotic content of the tablet is 500 mg. One tablet delivers 500 mg combined weight of the actives, intended for the treatment of a dog weighing 40 kg. A single dose is given twice daily usually for between 5 and 7 days. The product contains an artificial roast beef flavour. The application was made in accordance with Article 13(1) of Directive 2001/82/EC as amended by 2004/28/EC, claiming essential similarity with the reference product, Synulox Palatable Tablets 500 mg (Pfizer Ltd.), marketed in the UK. For this type of application, applicants are exempted from the usual requirement to produce evidence of safety and efficacy, if they show that the proposed product is a generic veterinary medicinal product, performing in the same manner as an established reference product, authorised in the EU for not less than ten years. The generic product is required to have a comparable composition to the reference product, the same pharmaceutical form, and to perform equivalently in treated animals.

The 50 mg and 250 mg versions of Nisamox Palatable Tablets for use in dogs have already been authorised in the UK and other member states. The 500 mg tablet offers more convenient treatment for dogs weighing more than 20 kg.

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 product is 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 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 product contains amoxicillin 400 mg (as amoxicillin trihydrate) and clavulanic acid 100 mg (as potassium clavulanate) and excipients sodium starch glycollate, carmoisine lake, copovidone K24-36, syloid AL-1FP, magnesium stearate, microcrystalline cellulose, calcium carbonate, magnesium carbonate heavy and roast beef flavour.
The tablets are packaged in foil/foil blister strips of 5 tablets per strip. These strips are packaged in boxes containing 2, 4, 5 or 20 blister strips per carton. The particulars of the containers and controls performed are provided and conform to current guidelines.
The choice of the formulation is justified. Clavulanic acid is sensitive to degradation in the presence of water so the other ingredients have been chosen because they do not readily absorb water.

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

Active Substance
Both the amoxicillin trihydrate and the potassium clavulanate used comply with the European Pharmacopoeial monographs and additional limits on particle size have been applied to both actives. 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.

Other Ingredients
All excipients, with the exception of anhydrous silicon dioxide, carmosine lake and roast beef flavour, are the subject of European Pharmacopoeial monographs. The ingredient specifications comply with the requirements of

these monographs. Anhydrous silicon dioxide has a monograph in the USNF[1] which is the basis of the ingredient specification, the difference being that the limits are tighter than described in the monograph to ensure suitability in the product. 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 suppliers 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.

Packaging materials
The tablets are supplied in blister packs made of a PVC/polyamide coated aluminium laminate and aluminium foil. A specification and certificate of compliance with the European Pharmacopoeia and food contact regulations certifies the suitability of these materials.

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 substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance 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.

[1] United States National Formulary - the official publication, issued by the United States Pharmacopoeial Convention, that gives the composition, description, method of preparation, and dosage for drugs.

In-Use
The dosing recommendations include the use of half tablets. A recommendation that "any halved tablets should be returned to the open blister and used within one day" has been added to the SPC[2].

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf-Life:

Shelf-life of veterinary product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 24 hours.
Any divided tablet portion remaining after 24 hours should be discarded.

Special Precautions for Storage:

- Do not store above 25°C.
- Store in a dry place.
- Divided tablets should be stored in the blister pack.

[2] Summary of Product Characteristics – Module 1 of this UKPAR

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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III.A Safety Testing

Pharmacological Studies

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, data on pharmacodynamics and pharmacokinetics are not required. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. However, the applicant has submitted data on a pharmacokinetic study in dogs

The study had a "crossover" design and involved two groups of dogs. The first group received a single dose of Nisamox Palatable Tablets 500 mg which had been crushed in order to permit accurate dosing. Justification was included for this dosage regimen. After eight weeks (considered to be a suitable time to allow all the active ingredients to disappear from their systems), they received a similar dose of the Synulox Palatable Tablets 500 mg, also crushed. The second group were treated in the same way but with the Synulox Palatable Tablets 500 mg being administered first, followed by the Nisamox Palatable Tablets 500 mg eight weeks later. This explains the term "crossover." Blood samples from the dogs were taken at a number of timepoints and the concentrations of amoxicillin and clavulanic acid in the samples were measured using validated methods. The results revealed that with respect to both the amoxicillin and clavulanic acid, the levels found in the blood were similar for both products. This finding was confirmed by statistical analysis.
The dissolution studies compared the rate of release of the two active ingredients from Nisamox Palatable Tablets 500 mg and Synulox Palatable Tablets 500 mg. The results revealed that the dissolution rates of the two active ingredients were similar for both products. The results were also within the specification detailed in the USP[3] monograph.

It can be concluded from these studies that the company has demonstrated that the Nisamox Palatable Tablets 500 mg complied with the official definition of essential similarity. Hence, no further studies were required to demonstrate the safety of the product to man or the environment.

Toxicological Studies

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, data on toxicology are not required. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

[3] United States Pharmacopoeia

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that skin contact is the most likely route of exposure to the product, and the allergic potential of amoxicillin is the major hazard. 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.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, this information is not required as it has already been presented for the reference product. Bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies, by means of an *in vivo* pharmacokinetic study and also by an *in vitro* tablet dissolution study.

Tolerance in the Target Species of Animals

The company also provided a report of the effects of Nisamox Palatable Tablets 500 mg on dogs. In this study commissioned by the applicant, dogs were given two daily doses of the tablets for eight consecutive days. The dogs were given either the recommended daily dose or three times the recommended daily dose. Some dogs were given a dose of the product that contained no active ingredient for comparative purposes. The dogs were closely observed by a veterinary surgeon for 1 hour after administration. Heart rate and body temperature were measured and recorded and blood samples were collected at intervals up to 16 days after initial dosing. A number of tests were carried out examining the blood cells and looking at the levels of specific substances and enzymes that are produced by chemical reactions in the body.

The results showed that there were no significant differences between any of the groups with respect to any of the parameters studied. This study showed that the product is well tolerated by dogs. Results from a palatability study were also provided. This demonstrated that tablets were often accepted by hand, even by sick dogs, and it justified the inclusion of the word “palatable” in the product name.

IV.B Clinical Studies

The application was based on the essential similarity of Nisamox Palatable Tablets 500 mg to the established Synulox Palatable Tablets 500 mg. The company demonstrated that the products were essentially similar by submitting the report of a bioequivalence study commissioned by the Applicant, that is a study which compared the two products in terms of how much of the active ingredients amoxicillin and clavulanic acid were absorbed into the bloodstream when the products were given as recommended, i.e. by mouth. This study, together with the dissolution study (described in section III of this discussion) demonstrated that Nisamox Palatable Tablets 500 mg complied with the official definition of essential similarity. This means that no further information was required to demonstrate the efficacy of the product or its safety for dogs.

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 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.

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