IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Noroclav 75 mg Chewable Flavoured Tablets for Cats and Dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0283/004/DC
Name, strength and pharmaceutical form	Noroclav 75 mg Chewable Flavoured Tablets for Cats and Dogs
Active substances(s)	Amoxicillin ,Clavulanic acid
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Date of Authorisation	29 January 2014
Target species	Cats, 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 *Staphylococcus* spp. Urinary tract infections caused by susceptible *Staphylococcus*s pp or *Escherichia coli*. Respiratory tract infections caused by susceptible *Staphylococcus* spp. Enteritis caused by susceptible *Escherichia coli*. Dental infections (e.g. gingivitis) 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.
ATCvet code	QJ01CR02
Concerned Member States	BE, BG, CY, CZ, DK, EL, ES, FR, HU, IT, LI, LT, LU, LV, NL, NO, PL, PT, RO, SE, SK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 applicant demonstrated that they will have an acceptable pharmacovigilance system in place to fulfil all pharmacovigilance obligations in accordance with the requirements of Directive 2001/82/EC, as amended.

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 products 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. Qualitative and Quantitative Particulars

The product contains 60 mg of amoxicillin and 15 mg of clavulanic acid, as amoxicillin trihydrate and potassium clavulanate, respectively, and the excipients sodium starch glycolate Type A, povidone K30, spray dried pork liver powder, yeast extract, colloidal hydrated silica, magnesium stearate and microcrystalline cellulose. The container/closure system consists of aluminium/aluminium blisters in outer cartons.
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 for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are amoxicillin trihydrate and potassium clavulanate, 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 materials. Batch analytical data demonstrating compliance with the specifications have been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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 has been provided.
Batch analytical data from the proposed production site has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Genetically Modified Organisms

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application was submitted under Article 13.3 (so-called Generic hybrid applications) of Directive 2001/82/EC, as amended. The tablet contains 60 mg amoxicillin (as amoxicillin trihydrate) and 15 mg clavulanic acid (as potassium clavulanate) respectively as active substances.

The reference product cited by the applicant for the 75 mg tablet strength in the RMS is Synulox Palatable Tablets 50 mg (Pfizer Healthcare Ireland – VPA 10019/036/001). The reference product used for the purpose of demonstrating bioequivalence is Synulox Palatable Tablets 50 mg.

The safety aspects of this product are considered to be identical to the reference product. The applicant referred to published information/data in support of the safety of the amoxicillin/clavulanic acid combination in both humans and animals (including the target species). It was accepted that the combination of amoxicillin and clavulanic acid has been in well established use in the proposed target species for many years.

Warnings and precautions as listed on the product literature are in line with those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

No proprietary pharmacodynamic data were provided. However, the applicant presented a review of the published literature in support of the pharmacodynamic properties of potentiated penicillin.

Amoxicillin is a beta-lactam antibiotic and its structure contains the beta-lactam ring and thiazolidine ring common to all penicillins. Amoxicillin shows activity against susceptible Gram-positive bacteria and Gram-negative bacteria. Beta-lactam antibiotics prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis. They inhibit the activity of transpeptidase enzymes, which catalyse cross-linkage of the glycopeptide polymer units that form the cell wall. They exert a bactericidal action but cause lysis of growing cells only.

Clavulanic acid is one of the naturally occurring metabolites of the streptomycete *Streptomyces clavuligerus*. It has a structural similarity to the penicillin nucleus, including possession of a beta-lactam ring. Clavulanic acid is a beta-lactamase inhibitor acting initially competitively but ultimately irreversibly. Clavulanic acid will penetrate the bacterial cell wall binding to both extracellular and intracellular beta-lactamases.

Amoxicillin is susceptible to breakdown by β-lactamase and therefore combination with an effective β-lactamase inhibitor (clavulanic acid) extends the range of bacteria against which it is active to include β-lactamase producing species. *In vitro* potentiated amoxicillin is active against a wide range of clinically important aerobic and anaerobic bacteria.

Toxicological Studies

The applicant presented a review of the published literature in support of the toxicity of potentiated penicillin. Given that bioequivalence between the proposed product and the reference product has been claimed, the published information cited by the applicant was considered supportive of the known acceptable toxicity profile for the active substances in the proposed formulation.

User Safety

The applicant provided a user safety assessment broadly in line with the guidelines.

The applicant provided an assessment of the possible routes of exposure and referred to known toxicity endpoints in respect of the active substances, and included a quantitative risk characterisation to compare exposure estimates with relevant toxicity end points. It was possible to conclude that exposure (dermal or accidental ingestion) to the highest tablet strength (500 mg) will not result in any greater risk to the user or a child than that already posed by the reference product or indeed similar human medicinal products (containing the same concentrations of active substances). It was concluded that the proposed products will not present an unacceptable risk to the user when used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

The warnings and advice proposed for inclusion in the SPC and product literature for Noroclav tablets are in line with those approved for the reference products in the RMS and are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in accordance with the VICH GL6 Guideline *'Environmental Impact Assessment for Veterinary Medicinal Products (VMPs) – Phase I'.* Using the Phase I decision tree, the applicant determined that the environmental risk assessment for Noroclav Tablets could stop in Phase I at question number 3 and this was accepted. It was concluded that the proposed products would not present an unacceptable risk for the environment when stored, used and disposed of in accordance with the recommendations included in the SPCs.
Warnings and precautions as listed on the product literature are considered adequate to ensure safety to the environment.

III.B Residues documentation
Residue Studies

Given that the product is not intended for administration to food producing species, no residue data were required.

IV. CLINICAL ASSESSMENT

The applicant presented a review of the published literature in support of the pharmacokinetic properties of potentiated penicillin. In addition to reference to published data, the applicant has conducted two *in-vivo* bioequivalence studies (one conducted in cats and the other in dogs) in order to demonstrate bioequivalence between Noroclav 50 mg Chewable Flavoured Tablets and the reference product Synulox Palatable Tablets 50 mg.

The applicant adequately validated the HPLC method for the determination of amoxicillin in canine and feline plasma over an appropriate concentration range in accordance with the relevant guidelines.

Based upon the data from the bioequivalence studies conducted, the candidate formulation Noroclav Chewable Flavoured Tablets was determined to be bioequivalent with the reference product Synulox Palatable Tablets for amoxicillin and clavulanic acid in cats.

Whilst both formulations could be accepted as being bioequivalent in dogs for clavulanic acid, the products were not demonstrated to be bioequivalent for amoxicillin in respect of the pharmacokinetic parameter AUC: the lower acceptance limit of the 90% confidence interval for AUC for amoxicillin in dogs was exceeded. In order to address possible implications of this finding for efficacy or possible resistance development, the applicant compared the mean plasma amoxicillin concentrations between formulations. For ß-lactam antimicrobials, time dependent bactericidal effect is of importance. It was demonstrated that the time for which the concentration of amoxicillin will be greater than any given MIC value (T>MIC) for target pathogens will be at least as long for the test articlewhen compared with the reference product. Based upon the data provided, it was concluded that exceeding the lower acceptance limit of the 90% confidence interval for AUC for amoxicillin in dogs is not expected to have a negative impact in terms of efficacy of the product or the possible development of resistance when compared with the reference product.

Bioequivalence of the higher tablet strengths (75 mg, 250 mg and 500 mg) was supported by way of *in-vitro* dissolution studies conducted in three different dissolution media (pHs 3.1, 4.5 and 6.8) in line with the relevant guidelines: the dissolution profiles of the three tablet strengths (both candidate and reference formulations) were sufficiently similar to permit the extrapolation of the findings from the *in-vivo* bioequivalence studies to the other tablet strengths.

Tolerance in the Target Species of Animals

Tolerance in the target species has been supported by two target animal tolerance studies (one conducted in cats and the other in dogs). Based upon the data provided, it can be concluded that an acceptable level of tolerance has been demonstrated in cats and in dogs following the administration of Noroclav Chewable Flavoured 50 mg Tablets and Noroclav Chewable Flavoured 250 mg Tablets respectively at a dose rate of up to 3xRTD for a period of 30 days.

Resistance

The applicant provided an overview from published literature of trends in resistance to the active substances amoxicillin and clavulanic acid. The proposed SPC was updated in line with the CVMP 'Revised guideline on the SPC for antimicrobial products' (EMEA/CVMP/SAGAM/383441/2005) to ensure that adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

No clinical data were provided on the basis that bioequivalence with the reference product was claimed. Although bioequivalence was not demonstrated for amoxicillin in respect of one of the pharmacokinetic parameters (AUC) in one of the proposed target species (dogs), satisfactory information/data was provided to demonstrate that the products would be therapeutically equivalent to the reference products.

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.

VI. 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 HPRA website.
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.

Changes:
None.