IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Clavucill 200mg/50mg, tablets for dogs

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Clavucill 200mg/50mg, tablets for dogs
Active substances	Amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate)
Applicant	V.M.D.n.v/s.a. Hoge Mauw 900 B-2370 Arendonk Belgium
Legal basis of application	A generic application in accordance with Article 13(1) of Directive 2001/82/EC, as amended.
Date of Authorisation	28th February 2014
Target species	Dogs
Indication for use	Clinically, amoxicillin has been shown to be effective in treating a wide range of diseases of dogs including: skin disease (including deep and superficial pyodermas); soft tissue infections (abscesses and anal sacculitis); dental infections (e.g. gingivitis); urinary tract infection; respiratory disease involving upper and lower respiratory tract; enteritis.
ATCvet code	QJ01CR02

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 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 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. Qualitative and Quantitative Particulars

Each tablet contains 200 mg of amoxicillin and 50 mg of clavulanic acid as amoxicillin trihydrate and potassium clavulanate respectively and the excipients colloidal anhydrous silica, sodium starch glycolate, microcrystalline cellulose, erythrosine (E127) and magnesium stearate.
The container/closure system consists of aluminium foil strips consisting of polyester, laminating agent, aluminium foil, laminating agent and LD polyethylene.
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 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 material. Batch analytical data demonstrating compliance with this specification 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 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.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13.1 and bioequivalence with a reference product has been claimed, results of safety tests are not required.

The tablets contain Amoxicillin 200 mg and Clavulanic acid 50 mg as active substances.

The reference product is Synulox 250 mg Smakelijke tabletten (authorised in Belgium and equivalent to Synulox Palatable tablets 250 mg authorised in Ireland).

The applicant has provided the results of *in-vivo* bioequivalence studies to demonstrate bioequivalence between Clavucillin 50 mg and the reference product Synulox 50 mg in cats and between the higher tablet strength Clavucillin 250 mg and the reference product Synulox 250 mg in dogs.

The safety and toxicological aspects of this product are considered to be the same as for the reference product.

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

The applicant has referred to published literature concerning the *in-vitro* spectrum of activity of amoxicillin/clavulanate and MIC data for target pathogens. It is considered that the combination has a broad spectrum of activity against both Gram positive and Gram negative bacteria.

Toxicological Studies

The safety and toxicological aspects of this product are considered to be the same as for the reference product.

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.

Resistance

The applicant has cited published literature in order to demonstrate adequate susceptibility of the target bacteria to the active substances. Although resistance to amoxicillin is widespread, resistance to the combination of amoxicillin and clavulanic acid is not.

It is accepted that the risk for antimicrobial resistance development is no greater for the product than that which already exists for the reference product.

User Safety

The applicant has provided a user safety assessment in line with the relevant guideline. The concentrations of active substances included in the proposed product are the same as in the reference product.

Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product. It is concluded that the product will not present an unacceptable risk to the user when used, stored and disposed of in accordance with the recommendations included in the SPC.

Environmental Risk Assessment

Phase I
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that the product is only to be administered to non-food producing species. Consequently, no further assessment is required and the assessment may end in phase I.

No special warnings regarding the environment are required.

General 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 given the target species (dogs).

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13.1 and bioequivalence with a reference product has been claimed, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV. A Pre-Clinical Studies

Pharmacology

The applicant has provided the results of two proprietary *in-vivo* comparative bioavailability studies comparing the pharmacokinetics of amoxicillin and clavulanic acid in dogs and cats between the 250 mg and 50 mg tablets strengths of candidate and reference product formulations respectively.

From the results of both studies, it can be accepted that the candidate formulation is bioequivalent to the reference product formulation in both target species, with the exception of clavulanic acid for the parameter C_{max} in cats.
However, based upon the data presented, it is accepted that the product is therapeutically equivalent to the reference product.

In addition, the applicant provided the results of *in-vitro* dissolution studies which indicate that the product has a similar dissolution profile to the reference product.

Tolerance in the Target Species of Animals

No specific tolerance studies using the candidate formulation have been conducted. Instead, the applicant has referred to tolerance findings from the *in-vivo* bioequivalence studies. The absence of target animal tolerance studies investigating tolerance to the candidate formulation can be accepted and the tolerance findings from the bioequivalence studies were shown to be acceptable.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

This is a generic application submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended. As bioequivalence with a reference product has been claimed, no clinical studies were 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 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.

Safety/Efficacy Changes

Summary of change (CRN 7020393)	**Approval date**
Deletion of non-food producing target species - cat	March 2015