IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Clavusan 50 mg + 12.5 mg tablets for dogs and cats

PRODUCT SUMMARY

EU Procedure number	IE/V/0778/001/DC
Name, strength and pharmaceutical form	Clavusan 50 mg + 12.5 mg tablets for dogs and cats
Active substance(s)	Amoxicillin trihydrate, potassium clavulanate
Applicant	Alfasan Nederland B.V, (10980), Kuipersweg 9, 3449 JA Woerden, Netherlands
Legal basis of application	Hybrid application in accordance with Article 19(1)(a) of Regulation (EU) 2019/6
Date of Authorisation	08/03/2023
Target species	Dogs and cats
Indication for use	For treatment of infections caused by bacteria susceptible to amoxicillin and clavulanic acid including: skin disease (including deep and superficial pyodermas); soft tissue infections (abscesses and anal sacculitis); dental infections (e.g. gingivitis); urinary tract infections; respiratory disease (involving upper and lower respiratory tract); enteritis.
ATC vet code	QJ01CR02
Concerned Member States	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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 relevant articles of Regulation (EU) 2019/6. 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

The product contains 50 mg amoxicillin (as amoxicillin trihydrate) and 12.5 mg clavulanic acid (as potassium clavulanate) and the excipients crospovidone, povidone, sodium starch glycolate type A, cellulose microcrystalline, silica colloidal hydrated, magnesium stearate, saccharin sodium and vanilla flavor.
The container/closure system consists of oPA/Alu/PVC - PVC/Alu heat sealed blister containing 10 tablets each and packaged in cardboard boxes of 10, 30, 50, 100 or 250 tablets.

The choice of the formulation is 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 for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials
The active substances are amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate), which are 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 specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with the specifications has been provided.
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 has 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. Other Information
Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a hybrid application according to Article 19(1)(a) of Regulation (EU) 2019/6, and the data derived from bioequivalence studies conducted by the applicant have been accepted, the results of safety tests are not required. The reference product cited by the applicant is Synulox Palatable Tablets 50 mg (Zoetis Belgium S.A., VPA 10387/074/001) which was first authorised in the Reference Member State on 01/10/1997 in accordance with a full application dossier and for which the marketing authorisation remains valid. The reference product has been authorised for in excess of ten years and can therefore be accepted as a valid reference product in this hybrid application.
The safety aspects of this product are considered to be the same as the reference product.
Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III. SAFETY ASSESSMENT

Pharmacological Studies
The applicant provided a series of bioequivalence and dissolution studies.
Three well-conducted GLP-compliant *in-vivo* bioequivalence studies were conducted, which compared the candidate and reference formulations in dogs and cats. Plasma concentrations of amoxicillin and clavulanic acid were measured following single administration of the candidate and reference formulations by the oral route, with blood samples collected at appropriate time points.

In dogs, following administration of amoxicillin at 10 mg/kg bodyweight (test article), maximum plasma concentrations (C_{max}) of 8223 ng/ml were reached within 1.0 – 2.0 hours (T_{max}). Following administration of clavulanic acid at 2.5 mg/kg bodyweight, maximum plasma concentrations (C_{max}) of 3924 ng/ml were reached within 0.5 – 1.75 hours (T_{max}).
In cats, following administration of amoxicillin at 10 mg/kg bodyweight (test article), maximum plasma concentrations (C_{max}) of 9843 ng/ml were reached within 1.3 – 3.0 hours (T_{max}). Following administration of clavulanic acid at 2.5 mg/kg bodyweight, maximum plasma concentrations (C_{max}) of 4945 ng/ml were reached within 0.3 – 2.0 hours (T_{max}).
From the results of the bioequivalence studies conducted and the subsequent statistical analysis, it is accepted that the candidate product formulation is bioequivalent to the reference product formulation in both target species, with the exception of clavulanic acid for the parameter AUC_t. However, additional information was presented by the applicant, which considered the impact of this finding in terms of both safety and efficacy and it was concluded that the candidate formulation can be considered acceptable, in terms of both safety and efficacy, when compared with the reference product.
Additionally, the applicant provided the results of *in-vitro* dissolution studies, which indicate that the candidate product formulation has a similar dissolution profile to the reference product formulation.

Toxicological Studies
This application was submitted in accordance with Article 19(1)(a) of Regulation (EU) 2019/6 (a hybrid application). Based upon the results of the *in-vivo* bioequivalence studies and the additional information and data provided, the toxicological aspects of this product are considered to be the same as for the reference product. Accordingly, the results of toxicological studies are not required.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not present any greater risk to the user than that presented by the reference product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

Penicillins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reaction 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.
To avoid accidental ingestion, particularly by a child, unused part-tablets should be returned to the open blister space, inserted back into the outer packaging, and kept in a safe place out of the sight and reach of children.

Environmental Risk Assessment
Phase I
The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the product will only be used in 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

As this is a hybrid application according to Article 19(1)(a) of Regulation (EU) 2019/6, and the results of bioequivalence studies and additional supportive data have been accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.
In addition, taking into account the results of the bioequivalence studies, as well as bibliographic and other data supporting target animal tolerance, it is considered that the risk to the target species will be similar for both the test and the reference products. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
Adequate warnings and precautions appear on the product literature:

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at local/regional level. Use of the product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach. The association of amoxicillin/clavulanic acid should be reserved for the treatment of clinical conditions which have responded poorly to other classes of antimicrobials or narrow spectrum penicillins.
Cross-resistance has been shown between amoxicillin/clavulanic acid and β-lactam antibiotics. Use of the product should be carefully considered when susceptibility testing has shown resistance to β-lactam antibiotics because its effectiveness may be reduced.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to amoxicillin/clavulanic acid and may decrease the effectiveness of treatment with β-lactam antibiotics due to the potential for cross-resistance.

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.