

IPAR



**Publicly Available Assessment Report for a
Veterinary Medicinal Product**

Twinox 40 mg/10 mg chewable tablets for cats and dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0656/001/DC
Name, strength and pharmaceutical form	Twinox 40 mg/10 mg chewable tablet
Active substance(s)	Amoxicillin trihydrate, potassium clavulanate diluted
Applicant	Krka, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of Authorisation/ completion of procedure	28/04/2021
Target species	Cats and dogs
Indication for use	For the 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.
ATCvet code	QJ01CR02
Concerned Member States	AT, BE, DE, FR, IT, NL, PT

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**

The product contains 40 mg amoxicillin (as amoxicillin trihydrate) and 10 mg clavulanic acid (as potassium clavulanate, diluted) and the excipients cellulose, microcrystalline, magnesium stearate, silica colloidal anhydrous, sodium starch glycollate (type A), dried autolyzed yeast and erythrosine aluminium lake, E127.

The container/closure system consists of a blister formed of an aluminium foil, which consists of aluminium layer coated with OPA (Oriented Polyamide) film on one side and PE with desiccant on the other side and an aluminium sealing foil which consists of aluminium layer and PE coating.

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, diluted), 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 specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.

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 has 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 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 generic application according to paragraph 1 of Article 13 of Directive 2001/82/EC, as amended, 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 generic 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 adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

The applicant provided a series of bioequivalence and dissolution studies.

Two GLP-compliant *in-vivo* bioequivalence studies were conducted, which compared the pharmacokinetics of amoxicillin and clavulanic acid in dogs and cats using the 250 mg and 50 mg tablet strengths of the candidate and reference formulations respectively. 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), mean maximum plasma concentrations (C_{max}) of 7.31 µg/ml was achieved at approximately 1.37 hours. The mean terminal half-life was 1.21 hours. Following administration of clavulanic acid at 2.5 mg/kg bodyweight, mean maximum plasma concentrations (C_{max}) of 1.33 µg/ml was achieved at approximately 1.02 hours. The mean terminal half-life was 0.83 hours.

In cats, following administration of amoxicillin at 10 mg/kg bodyweight (test article), mean maximum plasma concentrations (C_{max}) of 5.87 µg/ml was achieved at approximately 1.59 hours. The mean terminal half-life was 1.18 hours. Following administration of clavulanic acid at 2.5 mg/kg bodyweight, maximum plasma concentrations (C_{max}) of 3.16 µg/ml was achieved at approximately 0.70 hours. The mean terminal half-life was 0.81 hours.

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 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 and also that the 500 mg tablet strength of the candidate product has a similar dissolution profile to the strengths of the candidate product formulation (50 mg and 250 mg) used for the purpose of demonstrating bioequivalence.

Toxicological Studies

This application was submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended (a generic 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 and cephalosporins may cause hypersensitivity (allergy) following 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 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 generic application according to paragraph 1 of Article 13 of Directive 2001/82/EC, as amended, and the results of bioequivalence and dissolution studies 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 in terms of 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:

Whenever possible, the amoxicillin/clavulanic acid combination should only be used based on susceptibility testing. Official, national and regional antimicrobial policies should be taken into account when the product is used. 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 other penicillins, due to the potential for cross-resistance. A trend in resistance of *E. coli* is reported, including multidrug-resistant *E. coli*.

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.