ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Clavaseptin 62.5 mg Palatable Tablets for Dogs and Cats
(Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Hungary, Ireland, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, UK)

Clavaseptin P 62.5 mg Tablets for Dogs and Cats
(France, Luxembourg)

Clavaseptin 62.5 mg – Tablets for Dogs and Cats
(Austria, Germany, Italy)

Clavaseptin 50 mg / 12.5 mg Tablets for Dogs and Cats
(Denmark, Finland, Sweden, Norway)

PuAR correct as of 06/02/2019 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0209/004/DX/001
Name, strength and pharmaceutical form	Clavaseptin 62.5 mg Palatable Tablets for Dogs and Cats
Applicant	Vetoquinol UK Ltd Vetoquinol House Great Slade Buckingham Industrial Park Buckingham MK18 1PA
Active substance(s)	Amoxicillin (as amoxicillin trihydrate) Clavulanic acid (as potassium clavulanate)
ATC Vetcode	QJ01CR02
Target species	Dogs and cats
Indication for use	Dogs: Treatment or adjunctive treatment of periodontal infections caused by bacteria susceptible to amoxicillin in combination with clavulanic acid i.e. *Pasteurella* spp, *Streptococcus* spp and *Escherichia coli*. Cats: Treatment of skin infection (including wounds and abscesses) caused by bacteria susceptible to amoxicillin in combination with clavulanic acid i.e. *Pasteurella* spp, *Staphylococcus* spp, *Streptococcus* spp and *Escherichia coli*.

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	Full bibliographic application in accordance with Article 13 (a) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	17th April 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Greece, Italy, Norway, Belgium, Spain, Poland, Bulgaria, Finland, Lithuania, Portugal, Cyprus, France, Luxembourg, Romania, Czech Republic, Hungary, Latvia, Sweden, Slovenia, Ireland, Germany, Denmark, Netherlands, Slovakia, Estonia.

I. SCIENTIFIC OVERVIEW

Clavaseptin 62.5 mg Palatable Tablets for Dogs and Cats contain the active substance amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate) in the ratio 4:1. The product should be orally administered at a dose rate of 10 mg amoxicillin / 2.5 mg clavulanic acid per kg body weight twice daily, i.e. 1 tablet per 5 kg body weight every 12 hours.

The product is an extension of the previous marketing authorisations for Clavaseptin 50 mg Palatable Tablets for dogs and cats, Clavaseptin 250 mg Palatable Tablets for dogs and Clavaseptin 500 mg Palatable tablets for dogs and is an addition of a new intermediate strength. Bioequivalence with the existing tablet strengths has been demonstrated.

The product is indicated for the treatment of periodontal infections in dogs and skin infections in cats, which are caused by bacteria susceptible to amoxicillin in combination with clavulanic acid. The product should not be used in animals that are hypersensitive to penicillins and is contraindicated for use in gerbils, guinea pigs, hamsters, rabbits and chinchillas.

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[1].

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. Composition

The product contains amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate) as the active substances and excipients brown iron oxide (E172), crospovidone, povidone K25, silicon dioxide, microcrystalline cellulose, liver aroma, yeast aroma, magnesium stearate and hypromellose.

The products are supplied in cartons of 10, 100, 250 or 500 tablets presented in aluminium/aluminium strip pack each containing 10 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of formulation is justified.

[1] SPC – Summary of Product Characteristics

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

The active substances are amoxicillin trihydrate and potassium clavulanate, are established active substances described in the European Pharmacopoeia. The active substance is 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 have been provided.

There are nine excipients used in the formulation and each has been used previously in veterinary medicines. Crospovidone, povidone K25, microcrystalline cellulose, magnesium stearate, hypromellose, have monographs in the European Pharmacopoeia and each complies with the requirements of the current edition of the Ph. Eur. Silicon Dioxide is the subject of a monograph in the German Pharmacopoeia (DAB). The colorant brown iron oxide E172 comply with the requirements of Directive 95/45/EC and is certified for food and pharmaceutical use.

The applicant provided raw material specifications for liver aroma and yeast aroma comprising tests of appearance, identity, pH, solubility and loss on drying. This is considered acceptable.

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

Not applicable.

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. The tests include identification and assay of the active substances, identification of impurities, uniformity of mass and microbial purity.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. For amoxicillin trihydrate a retest period of 3 years from one manufacturer and 6 years from the other manufacturer have been established. For potassium clavulanate a retest period of 48 months is supported.

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. The shelf life of the finished product as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale: 2 years.
- Shelf life after first opening the immediate packaging: 12 hours.
- Do not store above 25ºC.
- Return any halved tablets to the opened strip-pack and use within 12 hours.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Bioequivalence of the product with the reference products, Clavaseptin 50 mg and Clavaseptin 250 mg, can be assumed and pharmacology of the active substance has previously been addressed for these products. Cross reference is made to this data and no further data is required.

Toxicological Studies

Bioequivalence of the product with the reference products, Clavaseptin 50 mg and Clavaseptin 250 mg, can be assumed and toxicology of the active

substance has previously been addressed for these products. Cross reference is made to this data and no further data is required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which identified the main routes of exposure as skin, hand-to-mouth or hand-to-eye transfer from handling the tablet as well as accidental ingestion by a child.

The following precautions are listed on the SPC and product literature:

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, 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 great care to avoid exposure, taking all recommended precautions.
- If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the doctor this warning.
- Swelling of the face, lips or eyes or difficulty breathing are more serious symptoms and require urgent medical attention.
- Wash hands after handling the tablets.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in accordance with VICH guidance 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

The applicant has provided a dissolution study in place of an *in vivo* bioequivalence study for product in the target species. The study has demonstrated a similarity in the dissolution for the three products, Clavaseptin 62.5 mg, Clavaseptin 50 mg and Clavaseptin 250 mg, and therefore *in vitro* equivalence of all Clavaseptin 62.5 mg with the reference product is demonstrated.

On the basis of the dissolution study bioequivalence of the product with the reference products, Clavaseptin 50 mg and Clavaseptin 250 mg, can be

extrapolated and pharmacology of the active substance has previously been addressed for these products. Cross reference is made to this data and no further data is required.

Tolerance in the Target Species of Animals

On the basis of the dissolution study bioequivalence of the product with the reference products, Clavaseptin 50 mg and Clavaseptin 250 mg, can be extrapolated and tolerance in the target species has previously been addressed for these products. Cross reference is made to this data and no further data is required.

Resistance

On the basis of the dissolution study bioequivalence of the product with the reference products, Clavaseptin 50 mg and Clavaseptin 250 mg, can be extrapolated and cross reference has been made to resistance data supplied for the reference products. In addition a more recent epidemiological study has been provided, which concluded that there has been no decrease in efficacy of the combination, amoxicillin and clavulanic acid, over the last three years for treatment of the bacterial infection indicated in the SPC. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

On the basis of the dissolution study bioequivalence of the product with the reference products, Clavaseptin 50 mg and Clavaseptin 250 mg, can be extrapolated and clinical studies have previously been performed for these products. Cross reference is made to this data and no further data is 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.

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)