Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cefaseptin 75 mg Tablets for Dogs
Cefaseptin 300 mg Tablets for Dogs
Cefaseptin 750 mg Tablets for Dogs

Date Created: March 2016

PuAR correct as of 20/03/2019 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0541/001-3/DC
Name, strength and pharmaceutical form	Cefaseptin 75 mg Tablets for Dogs Cefaseptin 300 mg Tablets for Dogs Cefaseptin 750 mg Tablets for Dogs
Applicant	Vetoquinol UK Limited Steadings Barn Pury Hill Business Park Nr Alderton Towcester Northamptonshire NN12 7LS
Active substance(s)	Cefalexin (as cefalexin monohydrate)
ATC Vetcode	QJ01DB01
Target species	Dogs
Indication for use	For the treatment of bacterial skin infections (including deep and superficial pyoderma) caused by organisms, including *Staphylococcus* spp., susceptible to cefalexin. For the treatment of urinary-tract infections (including nephritis and cystitis) caused by organisms, including *Escherichia coli,* susceptible to cefalexin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Articles 13 (1) and 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23 September 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

Cefaseptin 300 mg Tablets for Dogs has been developed as a generic of Rilexine 300 mg under Article 13 (1) of Directive 2001/82/EC as amended. The reference product has been authorised in the UK since 2005. Cefaseptin 75 mg and 750 mg have been developed as generic hybrids of the reference product due to the difference in strength, under Article 13 (3) of Directive 2001/82/EC as amended. Bioequivalence has been shown through *in vivo* comparison of the 300 mg tablet with the reference product, and by extension, has been demonstrated through suitable dissolution studies for the remaining strengths.

The products contain cefalexin and are authorised for the treatment of bacterial skin infections and urinary tract infections, caused by susceptible organisms, in dogs. The product is contraindicated in rabbits, guinea pigs, hamsters and gerbils. It should not be used in cases of resistance to cephalosporins or penicillins.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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

[1] SPC – Summary of product Characteristics.

are indicated in the SPC. The efficacy [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain 75 mg, 300 mg or 750 mg cefalexin (as cefalexin monohydrate) as the active substance. The excipients are lactose monohydrate, povidone K30, croscarmellose sodium, microcrystalline cellulose, porcine liver powder, yeast, crospovidone and sodium stearyl fumarate.

The container/closure system consists of a PVC/ aluminium/ OPA blister containing 6 (Cefaseptin 750 mg product), or 10 tablets (Cefaseptin 75 mg and 300 mg products). Blisters are packaged in cardboard cartons. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of blending the active and excipients before wet granulation of the mixture. The granulate is dried and tabletted, finally the tablets are packaged into blisters. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is cefalexin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is supplied in accordance with Ph. Eur. Certificates of Suitability. 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.

All excipients, apart from yeast and porcine liver powder, are described in a pharmacopoeia and manufactured according to their respective Ph. Eur.

[2] Efficacy – The production of a desired or intended result.

Monographs. Data were provided for the excipients not described in a pharmacopoeia. Certificates of analysis have been supplied.

II.C.4. Substances of Biological Origin

Scientific data and certificates of suitability issued by the EDQM have been provided and 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.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include those for identification and assay of the active substance, average mass, disintegration, dissolution and microbiological quality.

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.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Retest periods are stated on the Ph. Eur. Certificates of Suitability.

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. Data were provided for batches stored at 30°C/65% RH for 12 months and 40°C/75% RH for 6 months. The proposed shelf life was supported.

Photostability and in-use stability data were also provided for the products. No significant changes were noted after broken and unbroken tablets were exposed to light. For the in-use stability study tablets were removed from the blister, halved or quartered, and tested after 16 or 48 hours. No significant changes were observed.

G. Other Information

Shelf life of the finished product as packaged for sale is 2 years.
Shelf life after first opening the immediate packaging is 48 hours for the 300 mg and 750 mg products, and 16 hours for the 75 mg product.
Store in the original package.
Return any part used table to the opened blister-pack.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As these are generic (300 mg product), and generic hybrid applications (75 mg and 750 mg products), according to Articles 13 (1) and (3) respectively, of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies

As these are generic and generic hybrid applications according to Article 13 (1) and (3) respectively, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

Studies of Other Effects

Several studies have been conducted on the sensitiser and irritant properties of the product to provide additional information for user safety.

Skin Sensitisation
A GLP and OECD compliant study was performed in mice to evaluate the potential of the formulation to cause delayed contact hypersensitivity reactions. Mice were divided into treatment groups and received either a 5% dose, 10% dose, 25% dose, a negative control or a positive control by daily application to the dorsal surface of both ears. Clinical examinations were made daily and any local reactions recorded. A Local Lymph Node Assay (LLNA) was also performed.

Results showed no abnormal clinical signs, no local and no ear thickening. The LLNA was used to measure the proliferative response of lymph node cells. In the highest treatment group there was some proliferation and a dose-relationship was established with the other two treatment groups. This was attributed to delayed hypersensitivity and it was concluded that the product is a weak skin sensitiser.

Acute Dermal Irritation

A study to determine the potential irritant or corrosive properties of the formulation was conducted in accordance with GLP and OECD guidelines. The product was placed as a fine powder on a moistened gauze pad and applied to the clipped skin of a male rabbit. The pad was held in place with a non-irritating dressing for 3 minutes, 1 hour and 4 hours before removal. Observations for clinical signs and local reactions were made 1, 24, 48 and 72 hours after removal. No abnormal clinical signs were noted. A slight erythema was noted on day 1 after prolonged exposure. No other local reactions were seen, therefore the product was classed as non-irritant.

Acute Eye Irritation

A GLP and OECD compliant eye irritation study was performed in white rabbits. A small amount of the product was administered as a fine powder to the conjunctival sac of the left eye, whilst the untreated right eye acted as the control. After an hour both eyes were rinsed with 0.9% NaCl. Observations for clinical signs and ocular reactions were made 1, 24, 48 and 72 hours after removal. Moderate to marked chemosis and redness of conjunctiva were noted 1 hour after application. Other reactions included a slight iris lesion. All reactions resolved by the final day. It was concluded the product is not an eye irritant.

Observations in Humans

Cefalexin is used in human medicine and is generally considered safe, with mild, transient side effects, mostly concerning the gastrointestinal tract. Administration can result in a hypersensitivity reaction, including urticarial, pruritis, fever, eosinophilia, angioedema, joint pain, shock and toxic epidermal necrolysis. These reactions can be serious and occur in approximately 5% of patients administered a cephalosporin. Hypersensitivity reactions are more common in those with a history of allergies, particularly to penicillin.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the main routes of exposure will be through dermal contact when administering tablets, with possible hand to mouth or hand to eye transfer, and through accidental ingestion by a child. 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 injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporin and vice versa. Allergic reactions to these substances may occasionally be serious.
    1. Do not handle this product if you know you are sensitised or if you have been advised not to work with such preparations.
    2. Handle this product with great care to avoid exposure, taking all recommended precautions. Wash hands after use.
    3. 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 in breathing are more-serious symptoms and require urgent medical attention.

Environmental Safety

An Environmental Risk Assessment (ERA) has been submitted. The ERA was conducted in accordance with VICH and CVMP guidelines.

Phase I:
The product will only be used to treat individual dogs and as a result environmental exposure will be low. As the product is only intended to treat non-food animals a Phase II ERA was not required.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The pharmacodynamics of the products are the same as the reference product. Bioequivalence with the reference product has been demonstrated, therefore no further data are required.

Pharmacokinetics
An *in vivo* bioequivalence study was provided for Cefaseptin 300 mg tablets in support of the generic application. In addition, *in vitro* dissolution data were provided for two homothetic strengths, Cefaseptin 75 mg and Cefaseptin 750 mg tablets, for comparison. Further bioequivalence studies were not required.

Bioequivalence Study
A bioequivalence study was performed to compare the 300 mg test product with the reference product. A GLP compliant study was conducted using 12 male dogs, divided into two groups using a two-period, two-sequence cross-over design with a 14 day wash out period. A single dose of 15 mg/kg of each product was administered orally following overnight fasting. Dogs received either the test or reference product on day 0, receiving the other product on day 14. Blood

samples were collected for analysis before treatment and at regular intervals up to 48 hours post-treatment.

Pivotal pharmacokinetic parameters, AUC[3] and C_{max}[4], were determined from the blood plasma. Analysis of variance (ANOVA) was performed on the log transformed data and 90% confidence intervals (CI) were determined. The predefined acceptance criteria for the 90% CI was 80-125%.

The results show a similar pharmacokinetic profile for both products. The 90% CI fell within the predefined acceptance limits for both parameters, therefore bioequivalence with the reference product is accepted.

Dissolution Study
A comparative dissolution study has been submitted to compare the dissolution profiles of the 3 different tablet strengths to determine their *in vitro* equivalence. The dissolution studies were conducted using 3 different dissolution media, at 3 3 different pH values (pH 1.2, 4.5 and 7.5). Samples were collected at 5, 10, 15 and 30 minute intervals and cefalexin content in the dissolution media was determined.

The results showed similar dissolution profiles for the 3 dosage strengths. *In vitro* equivalence of all strengths has been satisfactorily demonstrated, therefore bioequivalence, as shown between the reference product and 300 mg tablet, can be extrapolated to the 75 mg and 750 mg tablet strengths.

Tolerance in the Target Species

As these are generic (300 mg product), and generic hybrid applications (75 mg and 750 mg products), according to Articles 13 (1) and (3) respectively, of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of tolerance studies are not required. In addition, the product was well tolerated in the *in vivo* bioequivalence study.

Resistance

As these are generic and generic hybrid applications according to Article 13 (1) and (3) respectively, and bioequivalence with a reference product has been demonstrated, resistance date is not required. Resistance has been identified to cefalexin and information on the resistance mechanisms has been included in the SPC.

The main resistance mechanisms include the production of cephalosporinases which cause hydrolysis of the β-lactam ring, decreased affinity for penicillin-binding proteins and efflux pumps remove the antibiotic from the bacterial cell, as well as changes in porins to reduce diffusion of the antibiotic into the cell. Cross resistance exists between antibiotics belonging to the β-lactam group due

[3] AUC – Area under the curve
[4] C_{max} – Maximum plasma concentration

to similarities in structure. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

As these are generic (300 mg product), and generic hybrid applications (75 mg and 750 mg products), according to Articles 13 (1) and (3) respectively, of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of clinical trials are not 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 of the product(s) is favourable

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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.

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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.

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