ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cephorum 250 mg Film-Coated Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0411/001/MR
Name, strength and pharmaceutical form	Cephorum 250 mg Film-Coated Tablets for Dogs
Applicant	Forum Animal Health Limited Crown House 2-8 Gloucester Road Redhill Surrey RH1 1FH
Active substance(s)	Cefalexin 250 mg(as cefalexin monohydrate)
ATC Vetcode	QJ01DB01
Target species	Dogs
Indication for use	The product is indicated for the treatment of urinary tract infections in dogs caused by *Klebsiella pneumoniae* and for the treatment of bacterial skin infections in dogs, when susceptible organisms are present.

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	Mutual recognition application in accordance with Article 13 (a) for well-established use, of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21 December 2011
Date product first authorised in the Reference Member State (MRP only)	11 June 1999
Concerned Member States for original procedure	France, Germany, Ireland, Portugal, Spain

I. SCIENTIFIC OVERVIEW

The product is indicated for dogs, for the treatment of urinary tract infection caused by *Klebsiella pneumonia* and for the treatment of bacterial skin infections when susceptible organisms are present. The recommended dose rate is 15 mg cefalexin/kg bodyweight twice daily. In severe or acute conditions, the dose may be doubled to 30 mg/kg, or given at more frequent intervals. The product literature describes the number of tablets per dose, for dogs of specific bodyweight. Treatment of five days is recommended, but this may be increase or shortened at the discretion of the veterinary surgeon. In dogs weighing less than 12 kg, dose or duration of dose should be in accordance with the benefit/risk assessment of the responsible veterinary surgeon.

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.

[1] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains cefalexin monohydrate, corresponding to 250 mg cefalexin per tablet. The excipients are titanium dioxide (E 171), povidone K25, sodium starch glycolate (Type A), magnesium stearate, macrogol 6000, lactose monohydrate, hypromellose, talc, peppermint oil and saccharin sodium dihydrate.

The container/closure system consist of white polproylene securitainers with white polyethylene snap on caps containing 50, 100 or 250 tablets and PVC/PVDC – aluminium foil blister packs containing 10 strips of 10 tablets each or 8 strips of 14 tablets each. The particulars of the containers and controls performed are provided and conform to the regulation.

The absence of preservative 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 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 substance is cefalexin, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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 are monographed in the Ph. Eur. A certificate of analysis was received for each component of the packaging demonstrating compliance with the specification.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Statements were provided which complied with the relevant guidelines on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

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. 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. Tests include those for tablet embossing, colour, odour, identification of active substance, dissolution, loss on drying and by-products and degradation products.

G. Stability

Stability data on the active substance and finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Do not store above 25°C.
Protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant provided bibliographical data, this was acceptable. Cefalexin is a member of the cephalosporin group of antibiotics, which contain a β-lactam ring, conferring a mode of action similar to that of the penicillins. The drug is therefore a structural analogue of the reactive portion of the bacterial cell wall, peptidoglycan, which interferes with the cross-linking of peptidoglycan polymers. It is also postulated that the active substance causes de-inhibition of bacterial autolysins, causing cell lysis. First generation cephalosporins, which include cefalexin are very active against Gram-positive cocci, and also have activity against a range of Gram-negative bacteria.

Pharmacokinetics

The applicant provided bibliographical data, this was acceptable. Cefalexin is suitable for oral administration, being acid-stable. Absorption is rapid and

extensive in all species. Distribution is wide, crossing the placenta, but showing poor penetration into the cerebro-spinal fluid. Metabolism is minimal, with excretion predominantly via the urine.

Toxicological Studies

Single dose toxicity

The applicant provided bibliographical data, this was acceptable. Adverse effects seen in a study which included dogs were emesis (at doses of >0.5 g/kg cefalexin in dogs), loss of co-ordination and tremors. 1 g/kg was seen to be lethal to three out of four dogs in the study. An LD_{50}[2] of 0.8 g/kg was noted for dogs in further study.

Repeated dose toxicity

A study was reported for rats receiving 250, 500 or 1000 mg/kg cefalexin with no adverse effect on growth over one year. In a further study dogs were dosed orally with 100, 200 or 400 mg/kg for one year. Salivation was a common side-effect when 200 or 400 mg/kg was administered. An occasional emetic response was seen at all three doses. Bodyweight, haematology and histopathological findings were normal.

Other Studies

Reproductive toxicity

In both rats and dogs given a single dose of cefalexin, antibiotic activity was observed in the milk of females, and within the foetuses and amniotic fluid of rats. In a further study, it was concluded that daily oral administration to rats of 250 or 500 mg/kg prior to and during pregnancy, or to mice and rats during organogenesis had no adverse foetal effects. High levels of cefalexin (800-1600 mg/kg bodyweight/day had an effect on implant in mice, the number of live foetuses and development of skeletal structure. There was no evidence of specific teratogenic effects. In rabbits, no teratogenic effects were noted at 100-200 mg/kg bodyweight/day, but 400 mg/kg bodyweight/day increased the number of foetuses showing retardation. Doses of 600 mg/kg bodyweight/day led to abortion and death, but there were no teratogenic effects.

Embryotoxicity including teratogenicity

Inhalation exposure to rats did not cause embryotoxic or teratogenic effects. A further investigation involving 80 pregnant women with bacteriuria (250 mg three times a day for seven days), did not find evidence of foetal toxicity.

[2] LD_{50}- the median lethal dose

Studies of other effects
The publicly available Safety Data Sheet revealed that cefalexin hydrochloride or cefalexin monohydrate were non-irritant to the skin of rabbits but slightly irritant to the eyes of rabbits.

Observations in Humans

The active substance has been utilised in human medicine for several decades, with a low rate of adverse effects, which may include vomiting, abdominal pain and diarrhoea. Nephrotixicity is rare compared to other incidences with other cephalosporins. The most common adverse event is hypersensitivity, with an incidence of 4-15%. More hypersensitivity is seen in patients who are hypersensitive to penicillin. Skin rashes may occur, and there were two incidences of toxic epidermal necroylsis, one of which was fatal. Neutropenia and eosinophillia have also been observed, along with reversible haemolysis. Anaphylaxis is rare.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which claimed that because the active substance has been widely used, warning and precautions as cited on the SPC and product literature are acceptable. It was agreed that 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 cephalosporins and vice versa. Allergic reaction 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 be in contact with such preparations.
2. Handle this product with great care to avoid exposure taking all recommended precautions.
3. 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 in breathing are more serious symptoms and require urgent medical attention. In case of accidental ingestion, seek medical attention immediately showing the physician this information.

Wash hands after use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that because the product is only intended for administration to dogs for a short period of time, the product is not expected to pose a risk to the environment when used as recommended.

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

Pharmacodynamics

The SPC cites appropriate MIC[3] data, in relation to the *in vitro* susceptibility of canine urinary, skin and pyoderma bacteria:-

Pathogen	**MIC_{90}** (µg/ml)
S. intermedius	0.5 to 8
S. aureus	2 to 8
E. coli	2 to 16
Beta haemolytic *Streptococcus* spp. (86)	2

The MIC_{90} value of cefalexin against *Klebsiella pneumoniae* isolated from urinary tract infections in dogs is 4 µg/ml.

Pharmacokinetics

The SPC cites appropriate data:-

After oral administration, 60 to 80% of cefalexin is absorbed from the small intestine. The delay reported between administration and beginning of absorption is approximately 20 minutes and differences in mean AUC[4], C_{max}[5], and T_{max}[6] are not significantly affected by food administration concomitant to treatment with cefalexin.

Dose administered (mg/kg)	15
Cmax (µg/ml)	17.6
Tmax (min)	158
AUC (µg.h/ml)	73.5
Half life (min)	107

Protein binding is low at 18%. Cefalexin is widely distributed into a variety of tissue fluids, including bile, synovial and pericardial fluid. The passage into

[3] MIC – Minimum inhibitory concentration.
[4] AUC – Area under the curve.
[5] C_{max} – Maximum plasma concentration.
[6] Tmax – Time at which maximum plasma concentration observed.

interstitial tissue, as demonstrated in wound fluid concentration, peritoneal fluid and skin blisters is generally good.

Cefalexin is minimally metabolized and primarily excreted via the renal route, around 70% of an oral dose is excreted into the urine in 24 hours in the dog. It is important to note that cefalexin concentrations obtained in urine are well above plasma concentrations, and similarly concentrations in bile may be up to four times higher.

Tolerance in the Target Species of Animals

A number of literature references were provided which gave an overview of the safety profile of the cephalosporins. A similar, but not identical adverse reaction profile to that seen with penicillins was described. The warnings in the SPC are sufficient.

Resistance

Sufficient published data were received for this section. Adequate warnings and precautions appear on the product literature:-

- The most prevalent resistance mechanism among gram-negative bacteria to cefalexin is due to the production of various beta-lactamases (cephalosporinase) that cause inactivation. Resistance in gram-positive bacteria often involves a decreased affinity of the PBPs (penicillin-binding proteins) for beta-lactam drugs. Efflux pumps, extruding the antibiotic from the bacterial cell, and structural changes in porins (reducing passive diffusion of the drug through the cell wall), may contribute to bacterial resistance.

- Cross-resistance (involving the same resistance mechanism) exists between antibiotics belonging to the beta-lactam group due to their similar structures. This occurs with beta-lactamase enzymes, structural changes in porins or variations in efflux pumps. Co-resistance (involving different resistance mechanisms) has been reported in *E. coli* due to a plasmid with resistance genes.

IV.B Clinical Studies

A number of bibliographical references were submitted for this section to support the approved indications for the treatment of skin and urinary infections, and this was considered sufficient for this type of application. The data supported the use of the product as described in the approved SPC.

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)