LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

MUTUAL RECOGNITION

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Kefavet vet 250 mg and 500 mg film coated tablets

MODULE 1

PRODUCT SUMMARY

EU Procedure number	SE/V/114/01-02/E03
Name, strength and pharmaceutical form	Kefavet vet 250 mg and 500 mg film coated tablets
Applicant	Oy Medfiles Ltd
Active substance(s)	cefalexin monohydrate
ATC Vetcode	QJ01DB01
Target species	Dog
Indication for use	Treatment of urinary tract infections and recurring severe dermatological infections caused by bacteria sensitive to cefalexin.

Kefavet vet 250 mg and 500 mg film coated tablets	SE/V/114/01-02/E03
Oy Medfiles Ltd	Publicly available assessment report

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	2007-10-24
Date product first authorised in the Reference Member State (MRP only)	2000-09-22
Concerned Member States for original procedure	ES, IT and PT

I. SCIENTIFIC OVERVIEW

The MAH of KEFAVET, Orion Pharma, requested Sweden to act as RMS for Kefavet, in a third repeat use Mutual recognition procedure including AT, BG, CY, DK, EL, FR, IE and IS as CMS. Initially a mutual recognition procedure (SE/V/110/01-02/MR) was performed in 2006, including ES, IT and PT as CMS. Furthermore, two repeat use MRPs (SE/V/114/01-02/E01, SE/V/114/01-02/E02) including BE, CZ, HU, PL, SK and EE, LU, LT, LV, NL, RO and SI as CMS were carried out in 2007 and 2009.

The active ingredient of KEFAVET is cephalexin, a first generation cephalosporin. The product, provided in two different strengths (250 mg and 500 mg) for the treatment of dermatological and urinary tract infection (UTI), was approved for market authorisation in Sweden, in September 22, 2000.
Previous to the authorisation of KEFAVET, a product containing cephalexin (CEFACEPTIN previous name: DERMACEF) was approved for the Swedish market with the indication treatment of dermatological infection in the dog. Thus, in accordance with article 13.3 of Directive 2001/82/EC, in the present application the applicant referred to the abridged application procedure for synonymous formulation. Data on bioavailability compared with the reference substance CEFACEPTIN (DERMACEF) and also with the cephalexin product RILEXIN is provided in the dossier and bioequivalence was sufficiently demonstrated. The comparison to RILEXIN was made due to this product was used in one of the clinical studies submitted in support for treatment of UTI. Since for the reference substance UTI is not an indicated use, bibliographic data was provided to demonstrate efficacy regarding this indication for KEFAVET.

Pursuant to section 5 and 7 of the Medical Products Act (1992:859), year 2010 renewal was granted of the marketing authorisation for KEFAVET VET based on the PSUAR period September 2006 to January 2010. The review of available safety data related to the period revealed no new safety issues and renewal was granted with unlimited validity.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains cefalexin monohydrate 250 mg and 500 mg, respectively and the excipients macrogol, magnesium stearate, sodium starch glycollate, povidone, lactose monohydrate, saccharin sodium, peppermint oil, titanium dioxide , talc and hypromellose.

The container/closure system consists of PVC/PVDC/Al-blisters.

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 on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is cefalexin monohydrate, an established substance 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.

Certificates of suitability issued by the EDQM have 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 have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance have been provided and assessed as part of the granting of the Certificate of Suitability 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 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.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies
As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The applicant has conducted an open three-way cross-over bioequivalence study between Kefavet, Dermacef and Rilexine after single-dose administration under fasting conditions. Bioequivalence between test and both reference products was demonstrated.

Toxicological Studies
As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

User Safety
No user risk assessment has been provided. As the user warnings in Section 4.5 of the SPC for Kefavet are similar to those for the reference product, the risk for the users of Kefavet is considered appropriately addressed. A user risk assessment for Kefavet was therefore not regarded as necessary. Minor changes to the SPC were agreed and they will be incorporated in a future variation application for the product.

Environmental Risk Assessment
An environmental impact assessment (EIA) in accordance with the VICH GL 6 was provided. Since Kefavet is intended for use in dogs and no particular concerns were identified the EIA stopped at Phase I. It can be concluded that unacceptable environmental impact is unlikely following the use of Kefavet in dogs.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

The applicant suggests the indication to comprise UTI and dermatological infection in the dog.

The applicant has conducted an open three-way cross-over bioequivalence study between Kefavet, Dermacef and Rilexine after single-dose administration under fasting conditions. A dose of 25 mg/kg was given to 12 beagle dogs. Plasma samples were collected pre-dose and up to 10 hours post-dose. Plasma concentrations of cefalexin were determined with a validated LC-MS/MS method. Bioequivalence between test and both reference products was demonstrated. The Kefavet tablets used in the bioequivalence study are not identical to those approved in this MRP since there has been a previous type II variation where the changes in composition have been accepted as not constituting a risk of bioinequivalence.

Since dermatologic infection is an approved indication for CEFACEPTIN, and bioeqvivalence was demonstrated between the two products the indication dermatological infection for KEFAVET is fully justified. Complementary documentation on the efficacy of cephalexin for treatment of UTI, is added in the dossier. This documentation is not to extensive, including quite few animals and the trials performed mainly without a control group. In one of the previous repeat use MRP (SE/V/114/01-02/MR) this issue was discussed and further information related to susceptibility to relevant bacteria, risk for resistance development and the appropriateness of the recommended posology was provided by the applicant and this information was considered sufficient to justify the UTI claim. Thus, the presented documentation demonstrates that cephalexin treatment of urinary tract infection caused by *K pneumoniae, E Coli* and possibly other gram negative and gram positive bacteria species is associated with a high cure rate. In addition, cephalosporins are well known in the treatment of UTI and the pharmacokinetics of cephalexin is favourable. Thus, taken together the documentation can therefore be regarded as sufficient. Since bioequivalence was demonstrated, tolerance is regarded to be similar to previously approved products containing the same active substance.

The CMS included in the current repeat use application accepted market authorization. Minor changes to the SPC were agreed and they will be incorporated in a future variation application for the product.

Kefavet vet 250 mg and 500 mg film coated tablets	SE/V/114/01-02/E03
Oy Medfiles Ltd	Publicly available assessment report

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 risk benefit 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

Quality changes

Summary of change (Application number)	Section updated in Module 3	Approval date

Safety/efficacy changes

Summary of change (Type; application number)	Section updated in Module 3	Approval date