ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Therios 300 mg Palatable Tablets for Dogs
Therios 750 mg Palatable Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0347/001/MR UK/V/0347/002/MR
Name, strength and pharmaceutical form	Therios 300 mg Palatable Tablets for Dogs Therios 750 mg Palatable Tablets for Dogs
Applicant	Sogeval SA 200 Route de Mayenne Laval BP2227 France 53022
Active substance(s)	Cefalexin
ATC Vetcode	QJ01DB01
Target species	Dogs
Indication for use	For the treatment of bacterial skin infections in dogs (including deep and superficial pyoderma) caused by organisms sensitive to cefalexin. For the treatment of urinary tract infections in dogs (including nephritis and cystitis), caused by organisms sensitive to cefalexin.

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	Generic applications in accordance with Article 13 (1) and 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	29th March 2010
Date product first authorised in the Reference Member State (MRP only)	27th February 2009
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway* Poland, Portugal, Spain, Sweden.

* 750 mg strength only. Added via MRP Repeat Use procedure.

I. SCIENTIFIC OVERVIEW

Therios 300 mg and 750 mg Palatable Tablets for Dogs are intended for the treatment of a variety of bacterial infections. Specifically, the product may be used for the treatment of bacterial skin infections in dogs (including deep and superficial pyoderma), caused by organisms sensitive to cefalexin, and also to treat urinary tract infections in dogs (including nephritis and cystitis) caused by cefalexin sensitive organisms. Therios 300 mg and 750 mg Palatable Tablets for Dogs are generic and hybrid products respectively, for which applications were submitted under Article 13 (1) for the 300 mg product, and 13 (3) (for hybrid applications), for the 750 mg product. These Articles pertain to Directive 2001/82/EC, as amended. A hybrid application may contain information additional to that required for a generic product. The reference product is Rilexine 300 mg Tablets.

The dose for this product is 15 mg cefalexin per kg bodyweight twice daily. Treatment for urinary tract infection should continue over fourteen days, for superficial infectious dermatitis for fifteen days, and for at least twenty-eight days for deep infectious dermatitis. Should severe conditions be presented, the dose may be doubled. Tablets may be halved or quartered to permit correct dosing.

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. Composition

The product contains the active ingredient cefalexin, and excipients silica colloidal anhydrous, magnesium stearate, ammonium glycyrrhizate, biscuit flavour F07012, croscarmellose sodium, yeast and polyethylene glycol 6000. Therios 750 mg Palatable Tablets for Dogs do not have the same qualitative and quantitative composition as the reference product, however, these tablets are homothetic[a] to the 300 mg presentation which was shown to be bioequivalent to the reference product. Safety tests and dissolution studies contributed to the authorisation of the 750 mg tablet presentation.

The container system is a blister pack, composed of polyvinylchloride (PVC) film, heat-sealed with an aluminium cover foil. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of preservative are 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.

Manufacturing formulae for a 350 kg batch for both the 300 mg tablets and the 750 mg tablets were presented. The tablets are formed in a conventional manner, with the active substance quantity adjusted to account for its potency. All ingredients apart from cefalexin monohydrate are sieved and blended, then silica and magnesium stearate are added, followed by lubricant. The tablets are then compressed and blister packed.

In-process controls include analysis of the mass of the tablets, in addition to tests for thickness, hardness and friability. Batches were tested against the finished product specification, and process validation data were also presented. All results were acceptable. Data submitted with regard to impurities for the 300 mg tablet were also considered acceptable for the 750 mg tablet as the two products are homothetic.

[a] Exhibits essential similarity

C. Control of Starting Materials

The active substance is cefalexin, (as cefalexin monohydrate), 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. EDQM[b] Certificates of Suitablility (CEP) were supplied. The following excipients are described in the Ph. Eur: anhydrous colloidal silica, magnesium stearate, croscarmellose sodium, polyethylene glycol 600, and ammonium glycyrrhizate. These raw materials are appropriately tested prior to use.

Yeast and biscuit flavour do not have a Ph. Eur monograph, therefore the applicant designed their own in-house specifications test for these excipients. This was considered satisfactory.

The tablets are packaged into blister packs formed of polyvinylchloride (PVC) film, heat-sealed with an aluminium cover foil. Specifications were presented for the PVC film and aluminium foil and a CEP was also provided for the foil. This was considered satisfactory.

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

A declaration was provided that the finished product complies with the current version of the CPMP/CVMP guideline on TSEs. In addition, 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. A further declaration states that magnesium stearate and biscuit flavour are sourced only from vegetable-based ingredients. A UK Format 2 statement was also included, which controls the use of the small amount of skimmed milk and milk-derived lactose used.

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

[b] European Directorate for the Quality of Medicines.

provided demonstrating compliance with the specification. Control tests on the finished products include tests for appearance, hardness, friability, uniformity of dose, disintegration and dissolution tests, and microbiological analysis. All tests conform to Ph. Eur guidelines. Results of HPLC analysis for the 300 mg tablets were permissibly extrapolated to the 750 mg tablets as the 750 mg tablets were considered homothetic the 300 mg tablets.

G. Stability

Active Substance

No data on stability studies were provided for cefalexin monohydrate, as suitable data were provided by the active substance manufacturer. Cefalexin monohydrate has a retest period of three years when stored in polyethylene bags, in a fibreboard or cardboard drum. From a second manufacturer, the active substance has a retest period of four years or five years, (depending on formulation), when stored in a polyethylene bag, placed within a laminated aluminium bag, within a corrugated cardboard box.

Finished Product - Therios 300 mg Palatable Tablets for Dogs

Analyses are made identical to those performed on release of the product, with the addition of a check to test halving and quartering of the tablets. A test for impurities is also included. Stability studies were conducted on three pilot scale batches, stored in authorised commercial packaging. Storage conditions were thirty-six months under real time conditions, and six months under accelerated conditions. Some deterioration was observed, but the SPC recommends appropriate storage conditions. Data were also presented for three industrial scale batches, which mimicked the protocol used for the pilot scale batches. From these data, the recommendation not to store the tablets above 25°C was established.

In-use Stability - Therios 300 mg Palatable Tablets for Dogs

Data were provided from fresh and aged industrial scale batches. Samples were placed at 25°C/60%RH for up to forty-eight hours, and analysed at various time-points. Results contributed to the establishment of an in-use shelf-life of forty-eight hours for divided tablets, and this is reflected in the SPC. The product was found not to be light-sensitive, and a comparability study with Rilexine 300 mg tablets supported the proposed three year shelf-life.

Finished Product - Therios 750 mg Palatable Tablets for Dogs

Stability studies were performed on two pilot scale batches of product, stored in commercial packaging for thirty-six months at 25°C/60%RH, and stored for twelve months at 30°C/60%RH. Degradation products, breakability and microbial quality were analysed in both batches, and limits were considered acceptable with suitable warnings placed in the SPC. Stability data were also provided for two industrial scale batches, stored under VICH conditions for thirty-

six months at 25ºC/60%RH and for twelve months at 30ºC/65%RH. Results were acceptable and any disintegration reflected in directions in the SPC.

In-use Stability - Therios 750 mg Palatable Tablets for Dogs

Data were provided from one aged industrial scale batch. In-use samples were placed at 25ºC/60%RH for up to forty-eight hours. All results were within specified limits, confirming the SPC instruction that divided tablets should be discarded within forty-eight hours when stored in the blister pack. Comparison with Rilexin 300 mg tablets with regard to disintegration was permitted, as the products were considered similar.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the products as packaged for sale is three years. Shelf-life after first opening of the immediate packaging is forty-eight hours, and any unused divided tablet portions remaining should be discarded after forty-eight hours. Portions of tablets should be stored in the blister pack. The products should not be stored above 25ºC.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

The pharmacological and toxicological aspects of the 300 mg product are identical to the reference product, and the 750 mg product is homothetic to the 300 mg product. Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Other Studies

The applicant provided bibliographical data which show that all excipients are satisfactory for use in this type of product.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which includes the following advice:-

'Cephalosporins may cause sensitisation (allergy) following injection, inhalation, ingestion or skin contact. Sensitivity to penicillins may lead to cross-sensitivity 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. Wash hands after use.

- 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.

- In the event of accidental ingestion, particularly by a child, seek medical attention and show the doctor the leaflet.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as the products are to be supplied for dogs on an individual basis, a Phase 1 risk assessment was sufficient. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. Disposal advice on the product literature provides practical advice for the end user, (the dog owner).

III.B Residues documentation

These products are intended for non-food producing species, thus there was no necessity to provide data for this section.

IV CLINICAL ASSESSMENT (EFFICACY)

These are generic applications according to Article 13. Bioequivalence with the reference product has been demonstrated for Therios 300mg Tablets for Dogs, and the 750 mg tablet is considered homothetic to the 300 mg tablet, therefore

efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

The applicant provided bibliographical data describing the effects of food on the pharmacokinetics of cefalexin. The first reference article showed that when cefalexin was given to humans after food, the C_{max}[c] of the active substance reduced by approximately 40%, T_{max}[d] increased and AUC value was reduced by 10% compared to fasted subjects.

The second reference article cited a study in a small number of dogs where little difference was seen in measureable parameters between fed and fasted subjects, when cefalexin was administered at 30 mg/kg every twelve hours.

Even after food is given, the dose of cefalexin given at 15 mg/kg will effectively control relevant bacterial infection in the target species.

IV.A Pre-Clinical Studies

Pharmacology

Data were provided for a GLP-compliant *in vivo* bioequivalence study which compared Therios 300 mg Palatable Tablets for Dogs with Rilexine 300 mg Tablets. A suitable number of dogs were given a single dose administration of one tablet in a cross-over study with a wash-out period of seven days between treatments. Blood samples were taken at various time points and plasma cefalexin analysed by HPLC. A two one-sided hypothesis test was used compare the bioequivalence of the two products. Bioequivalence was established for C_{max}, an appropriate AUC value, and MRT. [e]

A dissolution study was performed in order to establish similarity of dissolution between Rilexene 300 mg Tablets, Therios 300 mg Tablets for Dogs and Therios 750 mg Tablets for Dogs. Studies were performed at pH 2.0, pH 4.5 and pH 6.8 using a paddle apparatus at a temperature of approximately 37°C to dissolve the tablets. 400 ml of diluent was used for Rilexene 300 mg Tablets and Therios 300 mg Tablets for Dogs, and 1000 ml of diluent was used for the Therios 750 mg Tablets for Dogs. Dissolution was studied at a variety of time points. It was demonstrated that the 750 mg product had a dissolution profile similar to that of the 300 mg tablet, for which bioequivalence with the reference product had already been demonstrated.

Tolerance in the Target Species of Animals

The applicant conducted a GLP-compliant target animal tolerance study using multiple oral administrations in the target species in order to evaluate the excipient ammonium glycyrrhizinate, not previously authorised for use in the UK. All other excipients are commonly used in veterinary medicinal products, and the

[c] Maximum plasma concentration of drug.
[d] Time after administration when maximum concentration of drug is attained.
[e] Mean residence time.

active ingredient is the same as that used in the reference product. There was therefore no necessity to investigate tolerance for other parameters. A suitable number of dogs were randomised into four groups for a blinded, twelve week study. Group 1 received 12.5 mg of ammonium glycyrrhizate/day, group 2, 25 mg/day, group 3, 50 mg/day and the fourth group received a placebo. Animals were monitored before and during treatment, and no significant adverse effects were noted. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Not applicable.

IV.B Clinical Studies

Laboratory Trials

The results of two palatability studies were presented. In the first study, a suitable number of animals were divided into four groups. Animals were given one of the following products:-

- Therios 300 mg Tablets for Dogs
- Therios 300 mg Tablets for Dogs (different batch number)
- Therios 300 Canin
- Rilexine 300 mg Tablets

Spontaneous intake was compared to assisted intake or refusal, all Therios tablets were found to be palatable.

A second study employed a four-way cross-over design. Tablets tested were:-

- Therios 300 mg Tablets for Dogs
- Petphos Sporting Dog
- Relixine 300 mg Tablets (negative control)
- Relixine 300 Observance globale (positive control)

Spontaneous intake was compared to assisted intake or refusal, Therios tablets were found to be palatable.

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)