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

Orbax Palatable Oral Suspension 30 mg/ml for Dogs and Cats

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0254/001/DC
Name, strength and pharmaceutical form	Orbax Palatable Oral Suspension 30 mg/ml for Dogs and Cats
Applicant	Schering-Plough Ltd Scering-Plough House Shire Park Welwyn Garden City Hertfordshire AL7 1TW
Active substance(s)	Orbifloxacin
ATC Vetcode	QJ01MA95
Target species	Dogs and Cats
Indication for use	Dogs: Treatment of uncomplicated bacterial cystitis due to susceptible strains of *E coli* and *Proteus mirabilis*, and treatment of skin and associated soft tissue infections (wounds and abscesses), associated with bacteria susceptible to orbifloxacin. Cats: Treatment of skin and associated soft tissue infections (wounds and abscesses), associated with bacteria susceptible to orbifloxacin.

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 application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	01 October 2008
Concerned Member States for original procedure	Austria Belgium Bulgaria Cyprus Czech Republic Finland France Germany Greece Hungary Ireland Italy Luxembourg Malta Poland Portugal Romania Slovakia Slovenia Spain Sweden

I. SCIENTIFIC OVERVIEW

Orbax Palatable Oral Suspension 30 mg/ml for Dogs and Cats contains the fluoroquinolone antibiotic, orbifloxacin, 30 mg/ml. Orbifloxacin is a known active substance and has been authorised as Orbax tablets in several member states since 2000.

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]. Refer to the SPC for relevant safety warnings. 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 substance orbifloxacin at 30 mg/ml and the excipients water for injections, lactic acid, methacrylic acid polymer, sodium hydroxide, sorbic acid, propylene glycol, colloidal silicon dioxide and malt extract.

The container/closure system is a 25 ml amber glass bottle, type 1, with a low density polyethylene 'Press-In Bottle Adaptor' (PIBA) and a 3 ml low density polypropylene syringe with graduations of 0.1 ml. The secondary packaging consists of a partitioned folding carton which houses the bottle and package insert on one side and the PIBA and syringe on the other side. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and presence of the 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.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

[1] SPC – Summary of Product Characteristics.

C. Control of Starting Materials

The active substance is orbifloxacin, an established active substance. 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.

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

No intermediate products are formed during the manufacture of this product.

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.

G. 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.

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 claim of a 30 day stability after broaching is based on a study of a batch broached and stored for 15 months at 25^{o}C/60%RH. A sample was withdrawn daily for 10, 20 or 30 days and the remaining product tested. The results demonstrated that the product is stable for up to 30 days when stored under ambient temperature and humidity.

H. Genetically Modified Organisms

Not applicable

I. Other Information

Pharmaceutical Warnings:
The veterinary medicinal product does not require any special temperature storage conditions.
Store upright.
Keep the container in the outer carton

Shelf life
Unopened – 2 years
Opened – 30 days after first opening.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has submitted a number of studies to determine the antimicrobial susceptibilities of a wide range of animal bacterial pathogens to orbifloxacin. A review of drug interactions has also been reported.

Quinolones impair bacterial DNA-metabolism by inhibition of the enzyme DNA gyrase. Mammalian cells also possess a gyrase (topoisomerase II) which has an affinity for quinolones but this is several thousand times lower than that of the bacterial gyrase.

The main pharmacodynamic features are incorporated in the SPC:

> Orbifloxacin is a synthetic, broad spectrum antibacterial agent from the class of fluoroquinolone carboxylic acid derivatives.
>
> Orbifloxacin is bactericidal with activity against mainly Gram-negative bacteria but also against some Gram-positive bacteria. The mode of action of the fluoroquinolones is through interference with the bacterial enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.
>
> Orbifloxacin has been shown to be effective against strains of *E.coli* and *P.mirabilis* in treating urinary tract infection in dogs.
>
> Clinical trials have shown the veterinary medicinal product to be effective against the following pathogens indicated in causing skin infections in dogs: *E.coli, Staphylococcus intermedius, Staphylococcus aureus,* and *Klebsiella pneumoniae*

Clinical trials have shown the veterinary medicinal product to be effective against the following pathogens indicated in causing skin infections in cats: *Staphylococcus intermedius, Staphylococcus aureus, Pasteurella multocida, Klebsiella pneumoniae, Streptococcus haemolyticus G, and Enterococcus spp.*

The pharmacokinetics of orbifloxacin are well described in the studies and published papers provided.

The oral absorption of fluoroquinolones is generally fast and substantial in man with peak serum concentrations reached after 1-2 hours and similar times have been observed in rodents, dogs and monkeys. The fluoroquinolones have a large volume of distribution and their binding to plasma proteins is low. The degree of metabolism of the fluoroquinolones varies widely from weak metabolism and elimination, mainly in the parent form in the urine, to more extensive metabolism and elimination as a metabolite. Most of the primary metabolites are active against bacteria, but often have a shorter half-life than their parent compound. Elimination is primarily via the kidney and secondly via the liver (in bile).

The data submitted show that orbifloxacin is rapidly absorbed following oral administration to dogs with rapid elimination in the urine and the reported data indicated that orbifloxacin was widely distributed and was unlikely to be significantly metabolised in the body.

Toxicological Studies

- Single Dose Toxicity

The applicant has submitted two studies in rats and dogs following oral administration. Orbifloxacin is of low acute toxicity in rats and dogs and is therefore unlikely to present an undue hazard to the animal.

- Repeated Dose Toxicity

The applicant has provided a number of repeat dose studies of varying treatment length in mice, rats and dogs following oral administration. Repeat toxicity of orbifloxacin derived NOELs ranging from 2 – 80 mg/kg bodyweight in different species and at different doses. Symtoms in the dog included gastrointestinal signs such as discolouration of the faeces (white/yellow), emesis, soft and/or mucoid faeces, and at high doses, hypersalivation, reduced food consumption, mild weight loss, glucosuria and lower urine pH. Symptoms observed at the highest dose level in the cat included mild gastrointestinal effects such as increased incidence of emesis, salivation, and soft, mucoid, and/or watery feces. A slight decrease in food consumption was also observed.

- Reproductive Toxicity, including Teratogenicity:

The potential of orbifloxacin to elicit adverse effects on reproductive potential, including fertility and reproductive performance and developmental toxicity has been examined in a number of studies. The studies have shown prenatal/postnatal toxicity and developmental effects at certain higher doses in

rats and rabbits. The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs and cats and therefore, the product should not be used during pregnancy and lactation or in animals intended for breeding. Orbifloxacin has been shown not to be teratogenic to rats and rabbits.

- Mutagenicity

Orbifloxacin has been investigated in a number of in vitro and in vivo mutagenicity studies. Five published papers were also provided. The applicant concluded that there is no mutagenic risk to the target species as the doses required to induce genotoxic effects in mammalian cells are significantly higher than for bacteria. The genetic toxicology profile of orbifloxacin is similar to that described for the fluoroquinolones approved for human medicines. The mutagenic potential is low even though bacterial DNA metabolism is a major target of their action.

- Carcinogenicity

Orbifloxacin has been investigated in a number of carcinogenicity studies in rodents. The two-year studies demonstrated that orbifloxacin was not carcinogenic when fed at daily dose rates of up to 200 mg/kg bodyweight.

Other Studies

- Irritation and Sensitisation

The applicant has submitted several studies to investigate the potential for irritation and sensitisation. Three of the studies were conducted using Orbax Oral Liquid which consists of a 30mg/ml solution of orbifloxacin in water, (a similar formulation to Orbax Oral Suspension but not identical) and the other three used micronised orbifloxacin.

- Toxicity to immature articular cartilage

The applicant has submitted two studies to address the potential for affects on articular cartilage in young dogs because toxicity to immature articular cartilage has been observed with other quinolones as reported in published papers. There were several studies: a one-month study which examined the effects of daily doses of 12.5 and 25 mg/kg bodyweight in young male and female dogs and two three-month studies were done to establish a NOEL using daily doses of up to 2 mg/kg bodyweight. The studies confirmed that orbifloxacin affects articular cartilage in young dogs particularly males, and a NOEL of 2 mg/kg bodyweight was defined in the three-month studies.

- Immunotoxicity

The applicant has submitted a published paper which reviews the effects of quinolones on the immune system. To date there is no evidence to show that they effect the bone marrow of animals or humans. There is some evidence that at low levels of quinolone concentrations, immune responses may be enhanced but this has not been proved and the clinical significance is not known.

- Studies on Metabolites, Impurities, Other Substances and Formulation.

The applicant submitted brief data on the other ingredients and justified that, because they are all commonly used in pharmaceutical tablet manufacture, they are safe and that the safety of the excipients and any metabolites formed, have been "tested" as part of the Target Animal Safety Studies submitted. This was considered to be acceptable.

Observations in Humans

The applicant has noted that orbifloxacin is not intended for human use and there are therefore no data. However, there is a concern of the potential for arthropathy in children and the applicant has submitted three published papers on other quinolones that address this concern. These references conclude that the quinolones induced arthropathy seen in juvenile animals is not found in children.

It is noted that structurally related fluoroquinolones approved for use in human medicines have a wide margin of safety, although adverse effects associated with these quinolone antibacterial have been known to cause joint erosions in immature animals and this has led to their contraindication in the treatment of children.

Other reported adverse effects of fluoroquinolones in human medicines are primarily CNS disturbances, (seizures, depression, dizziness, headaches) and gastrointestinal effects, (nausea, dyspepsia, diarrhoea) but these are usually relatively minor and transient.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. This identifies all potential routes of exposure of the operator to the product. The following user warnings have been included in the SPC and the product literature:

- Avoid skin and eye contact
- In case of accidental contact with skin, rinse affected area with copious amounts of water.
- In case of accidental contact with eyes, rinse with plenty of clean water.
- Do not handle this product if you have known hypersensitivity against substances in this product or to any other (fluoro)quinolones.
- Do not smoke, eat or drink when handling the veterinary medicinal product.
- Wash hands carefully after administering the veterinary medicinal product

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

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 environmental exposure to the product will not be extensive, the product is indicated for dogs and cats only and is for individual animals on veterinary prescription only. The controlled manner of administration offers extremely limited scope for environmental contamination.

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 conducted several pharmacodynamic and pharmacokinetic studies of which the conclusions are summarised in the SPC.

Pharmacodynamics
The bactericidal action of orbifloxacin results from interference with enzymes of DNA-gyrase and topoisomerase IV which are needed for the synthesis and maintenance of bacterial DNA. The applicant has provided MIC data from skin pathogens collected during their worldwide field trials in both cats and dogs. The MIC_{90} values for the most common isolates from the EU field trials for the demonstration of efficacy in relation to the skin claim are as follows:

Dog			Cat		
Pathogen	N	MIC_{90} µg/ml	Pathogen	N	MIC_{90} µg/ml
S. intermedius	69	1	*S. aureus*	67	2
S. aureus	27	2	*P.multocida*	61	1
Str. haemolytica	22	4	*S. intermedius*	19	4

Pharmacokinetics
Orbifloxacin is widely distributed to the tissues of dogs and cats. Orbifloxacin undergoes limited metabolism in both the dog and cat and in both species undergoes both renal and hepatic elimination.

Dogs:

The oral bioavailability of orbifloxacin in dogs is approximately 100%. Maximum plasma concentrations (C_{max}) of approximately 2.3 µg /ml are achieved within one hour after a 2.5 mg/kg oral dose. After single dose administration to dogs at 7.5 mg/kg bodyweight, a C_{max} of approximately 5.8 µg /ml is achieved within two hours. The plasma elimination half life is approximately 6 hours. The accumulation between doses given at 24 hour intervals is negligible.

Approximately 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 2.5 mg/kg dose, urine concentrations of orbifloxacin are approximately 100 μg/ml for approximately 12 hours after dosing. By 24 hours, urine concentrations of orbifloxacin are approximately 40 μg/ml. Plasma protein binding of orbifloxacin is low in the dog.

Cats:
After single dose administration to cats at 7.5 mg/kg bodyweight, maximum plasma concentrations (C_{max}) of approximately 3.4 μg /ml are achieved in approximately 2 hours. The plasma half-life ($T_{1/2}$) is approximately 8 hours

Tolerance in the Target Species of Animals

The applicant has conducted target animal tolerance studies using multiples of the recommended dose in the target species. Control animals were dosed with distilled water.

Dogs:
The effects in dogs of overdose have been investigated following dosing at 3x and 5x the dose level at 3x the intended treatment duration, as well as at 10x the dose level for the intended treatment duration. Symptoms observed include gastrointestinal signs such as discolouration of the faeces (white/yellow), emesis, soft and/or mucoid faeces, and at highest dose (75mg/kg/day) hypersalivation, reduced food consumption, mild weight loss, glucosuria and lower urine pH. In addition, one clinically normal high-dose dog had alterations in a variety of liver parameters. Symptomatic treatment and/or discontinuation of therapy should be considered if intolerance is observed.

Cats:
The effects in cats of overdose have been investigated following dosing at 1x, 2x, 6x and 10x the dose level at 3x the intended treatment duration. Symptoms observed at the higher dose level included mild gastrointestinal effects such as increased incidence of emesis, salivation, and at the highest dose level soft, mucoid, and/or watery feces. A slight decrease in food consumption has been observed. Symptomatic treatment and/or discontinuation of therapy should be considered if intolerance is observed.

Ocular safety was assessed. There were no electroretinographic changes and no visual deficits observed in any cat. At the exaggerated doses of 45.0 and 75.0 mg/kg/day, minimal ophthalmic changes were noted which consisted of tapetal hyperreflectivity, which correlated histopathologically with minimal swelling of photoreceptor cells; without any progression to other lesions associated with retinal degeneration or necrosis. Electron microscopy revealed swollen rod cells with disorganized disc material in the outer photoreceptor segments. If a visual deficit is suspected, discontinue use immediately.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

A number of references to known mechanisms of resistance to fluoroquinolones have been provided.

The SPC states:
Heavy reliance on a single class of antibiotic may result in the induction of resistance in a bacterial population. It is prudent to reserve the fluoroquinolones for the treatment of clinical conditions which have responded poorly to other classes of antimicrobials. Whenever possible, fluoroquinolones should only be used based on susceptibility testing.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

A study on the efficacy of orbifloxacin for the treatment of urinary tract infections used orbifloxacin tablets and compared the results to those of an already authorised product for this indication. Five days after the end of treatment, 73% of cases were evaluated as having an excellent clinical response to treatment with Orbax compared to 52% with the already authorised product. Bioequivalence has been demonstrated between the orbifloxacin tablets and Orbax Oral Suspension. Based on the information provided, a dosage of 2.5 mg/kg is the optimum dose of orbifloxacin tablets to treat urinary tract infections in dogs.

Two similar studies, one in dogs and one in cats, were conducted on the efficacy of orbifloxacin for the treatment of dermal wound infections. The studies compared Orbax Oral Suspension to a product already authorised for this indication. These studies demonstrated that when Orbax Oral Suspension was administered at 7.5 mg/kg SID for 5-13 days to dogs and cats with soft tissue infections, wound healing occurred in 96.3 % of cases in dogs and 93% of cases in cats. This was equivalent to the healing rate achieved with the comparative product. Based on the information provided, a dosage of 7.5 mg/kg is the optimum dose of Orbax Oral Suspension to treat skin and associated soft tissue infections in dogs or cats.

The incidence of Suspected Adverse Reactions to Orbax oral liquid in the study for dogs was low and consisted of gastrointestinal signs (vomiting, diarrhoea, soft faeces). The warnings in section 4.6 of the SPC are appropriate.

In the study in cats, the incidence of treatment related gastrointestinal disturbances was low and the warnings in section 4.6 of the SPC are considered to be adequate.

The claims on the SPC are fully supported and the warnings included are considered sufficient for this product.

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)