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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Veraflox (as published in July 2011). For information on changes after this date please refer to module 8.

1. Summary of the dossier

Veraflox is eligible for assessment under the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 as it contains a new active substance which has not been authorised in the Community for use in a medicinal product intended for use in animals.

Veraflox Tablets are intended for the treatment of dogs with the following infections caused by certain specified and susceptible pathogens: wound infections; superficial and deep pyoderma; acute urinary tract infections; and, as adjunctive treatment (to mechanical or surgical periodontal therapy) in the treatment of severe infections of the gingival and periodontal tissues.

Veraflox Tablets are also intended for the treatment of cats with acute infections of the upper respiratory tract caused by certain specified and susceptible pathogens.

Veraflox Oral Suspension is intended only for the treatment of cats with the following infections caused by certain specified and susceptible pathogens: acute infections of the upper respiratory tract; wound infections and abscesses.

The active substance of Veraflox is pradofloxacin, a third generation fluoroquinolone antibiotic (ATCvet code: QJ01MA). Pradofloxacin exerts its bactericidal effects by its interaction with enzymes responsible for major DNA functions.

The product is presented as 15 mg, 60 mg and 120 mg (pradofloxacin) tablets and also as a 25 mg/ml (2.5% w/v pradofloxacin) oral suspension. The route of administration is oral for both pharmaceutical forms.

The benefits of Veraflox are its enhanced broad spectrum antimicrobial activity when compared to other fluoroquinolones and the low incidence of resistance towards pradofloxacin. Veraflox is well tolerated in cats and dogs with mild transient gastro-intestinal disturbances, including vomiting, being observed only in rare cases in these animals.

Veraflox could be harmful to children ingesting the product accidentally. Therefore Veraflox Tablets and filled syringes of Veraflox Oral Suspension should be kept out of the reach and sight of children.

The GMP status of the dosage form manufacturing, assembly and release sites is satisfactory.

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The pharmacovigilance system in place complies with the requirements in the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products in Volume 9 of the Rules governing medicinal products in the EU.

2. Quality assessment

Composition

Veraflox Tablets are unremarkable in terms of their composition and include, in addition to the active substance, pradofloxacin, several conventional tablet excipients plus an artificial beef flavour to improve palatability to both cats and dogs. All dosage strengths are compressed from a common strength granulate, the tablets differing only in their weight and size.

The composition of Veraflox 25 mg/ml Oral Suspension is also unremarkable, and includes, in addition to the active substance, pradofloxacin, several excipients commonly used in oral suspensions including an antioxidant (ascorbic acid), preservative (sorbic acid) and a (vanilla) flavouring agent.

Container

Veraflox Tablets will be packed into blister strips formed from a polyamide/aluminium/polypropylene composite material sealed with a coated aluminium film.

Veraflox 25 mg/ml Oral Suspension will be filled into white, polyethylene bottles (15 ml and 30 ml) closed with a child resistant screw cap containing a polyethylene adapter. The 15 ml size (only) will be supplied with a polypropylene oral syringe graduated up to 2.0 ml.

Development Pharmaceutics

Tablets:

Based on a desired dose of 3 mg pradofloxacin/kg bodyweight (bw), three different tablet strengths were developed, 15, 60 and 120 mg. Divisible tablets (with score marks on both sides) were chosen to facilitate the administration of an accurate dose to animals of different weight. Capsule shaped tablets were chosen to facilitate their ingestion and swallowing by both of the target species. A flavour (artificial beef) is incorporated to mask the bitter taste of the active ingredient and to improve the palatability of the tablets and its content was optimised.

Pradofloxacin can exist in several crystal forms. The choice of the selected polymorph was justified. The particle size of the active substance was well controlled. Pradofloxacin is soluble in water, so it was not necessary to micronise the active substance.

All the excipients are well established and widely used in both human and veterinary medicinal products. Results of compatibility studies and stability studies have demonstrated that the excipients chosen have no significant impact on pradofloxacin or on other ingredients of the formulation. The quantities of each excipient and the manufacturing process have been optimised to produce tablets of optimal hardness, disintegration and dissolution.

The granulate homogeneity has been demonstrated on 3 production scale batches and tablets were compressed from these batches and tested. The tablets met all the relevant requirements of their specifications and also the relevant monographs of the European Pharmacopoeia (Ph. Eur.).

The choice of primary packaging for the tablets (aluminium/aluminium blisters) was justified.

Oral Suspension:

The aim of the development pharmaceutics was to manufacture a palatable, liquid formulation for oral administration to cats. Based on the desired dose of 5 mg/kg bw and considering a potential weight range of 0.25 kg to 10 kg as well as an application volume of 1 ml for a 5 kg animal, a formulation containing 25 mg/ml was developed. A flavouring agent (vanilla) is included in the formulation to mask the bitter taste of the active ingredient and to improve the palatability of the suspension.

Pradofloxacin can exist in several crystal forms. The choice of the selected polymorph for this pharmaceutical form was justified. The particle size of the active substance was well controlled. Pradofloxacin is soluble in water, so micronisation was not necessary. Consistency of pradofloxacin particle size in the suspension from batch to batch and on scale-up has been demonstrated, as has the stability of active substance particle size on storage over the claimed shelf-life (3 years) over challenging storage conditions, including short periods of freeze-thaw cycling.

The necessity for, and selection of, sorbic acid as a preservative in the formulation was justified, and its effectiveness demonstrated according by the Ph. Eur. method. Sorbic acid is a widely used preservative in human and veterinary medicinal products and also in foods. The artificial vanilla flavour is widely used in the food industry, complies with Council Directive 88/388/EEC for flavours and is included in the formulation to improve both its smell and taste in order to improve compliance in the cat. The other excipients were justified.

Veraflox 25 mg/ml Oral Suspension has shown a very high dissolution rate at both release and at all time points during the stability studies, independent of test conditions.

No incompatibilities between the active substance and the excipients or between any of the excipients in the formulation have been found, in any of the stability studies.

A standard polyethylene bottle with a polyethylene adapter and a child-resistant closure was chosen for this oral suspension. Filling overages are included to ensure that the stated volume can be withdrawn from the bottles and these have been justified. The 15 ml size container is supplied with a syringe (graduated up to 2.0 ml in 0.1 ml steps) which ensures the product meets the requirements of Ph. Eur. monograph 2.9.27 "Uniformity of mass of delivered doses from multidose containers".

Method of manufacture

Tablets:

The manufacturing process is typical for conventional tablets and is carried out with adequate in-process controls. Appropriate validation studies have been performed, the results of which demonstrate that the product is produced consistently and in accordance with the agreed specifications.

Oral Suspension:

The oral suspension manufacturing process is unremarkable and is carried out with adequate in-process controls. Appropriate validation studies have been performed, the results of which demonstrate that the oral suspension is produced consistently and in accordance with the agreed specifications.

Control of starting materials

Active substance (pradofloxacin)

Pradofloxacin, a fluoroquinolone carboxylic acid, is a brownish light yellow to yellow, fine crystalline new active substance. Its chemical name is 8-Cyano-1-cyclopropyl-7-(1S,6S)-2,8-diazabicyclo-(4.3.0)nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid. Due to the two chiral carbon atoms of the pyrrolopiperidine group, four enantiomeric forms (two pairs of enantiomers) can exist. The S,S-isomer has been chosen because of its high antimicrobial potency.

Pradofloxacin crystallizes in six modifications. Two hydrates, and a dichlormethane-solvate were observed. The amorphous form can exist at room temperature. Production of the chosen crystal modification is controlled during release testing of the drug substance. This form is stable under normal storage conditions and has been found to be most suitable for both the tablets and the oral suspension.

Pradofloxacin is not included in any pharmacopoeia so a detailed specification was provided which includes tests for appearance, identity, presence of the desired enantiomeric form; appearance of solution (clarity and colour), pH, assay, chemical purity, chloride, residual solvent content, sulphated ash, heavy metals, water content and microbial purity. The absence of a test and limits for particle size in the active substance specification has been justified as the manufacturing process has been demonstrated to reproducibly produce pradofloxacin of a consistently small particle size. The specification reflects all the relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitably described and validation studies are in accordance with the relevant VICH and EU guidelines. Impurity limits in the specifications are justified by batch history and toxicology studies.

The manufacturing process is described in sufficient detail and includes adequate in-process controls. Comprehensive specifications and control methods for the starting materials, reagents, solvents and auxiliary materials used during synthesis have been presented. All methods have been described and validated where necessary.

Special attention has been paid to the control of the enantiomeric and diastereomeric purity of the pivotal starting material. Although the content of residual solvents in the starting material are higher than usual in active substances for pharmaceutical use, residual solvents are controlled to the VICH limit in the active substance specification for pradofloxacin, and this was considered satisfactory. Batch analysis data demonstrate the levels of residual solvents in pradofloxacin are consistently low.

Stability data from three batches of pradofloxacin (produced at the proposed final production site) are available following storage for up to 36 months at 25°C/60% RH and 40°C/75% RH. Additional data from follow up stability studies support the findings. Testing methods were identical to those described for the active substance.

Pradofloxacin was found to be very stable to heat and acidic hydrolysis. 7-hydroxy-8-cyano-fluoroquinoline carboxylic acid was found to be the main degradation product under alkaline conditions. When exposed to light (1.2 million lux hours and >200 Watts/m^2 according to the VICH guideline) in the solid state only surface colouration takes place. However, when exposed to light in solution (0.1% in water) considerable degradation occurs and it is difficult to identify the cascade of products formed.

No special storage conditions are therefore required for pradofloxacin, but it should be stored in a dry place and protected from light, especially if the container has been opened. The proposed retest period has been justified.

Excipients

Tablets:

Conventional pharmaceutical excipients are used and they all comply with the relevant Ph. Eur. monographs, except the artificial beef flavour (which is not the subject of a pharmacopoeial monograph and is therefore the subject of an in house monograph). Typical certificates of analysis are presented for each excipient and these demonstrate their compliance with the stated specifications.

The artificial beef flavour consists of three components: hydrolysed vegetable protein; hydrogenated vegetable oil; and natural flavouring. The hydrolysed vegetable protein and the hydrogenated vegetable oil are produced from human-grade soybeans. The natural flavour is sourced from human-grade pork livers. The manufacture of each of the three components and the flavour itself is adequately described. The in-house specification for the artificial beef flavour contains the following quality characteristics: appearance, odour, protein content, particle size, fat content, moisture and microbiological purity. The test methods are all described. Batch analysis data are in agreement with the quality specifications. The artificial beef flavour is gamma-irradiated to inactivate potential viruses and micro-organisms. Full details of the process and its validation are provided. The CVMP concluded that the risk of viral contamination is negligible considering the origin of the raw material, the manufacturing process and controls and the intended use.

Oral Suspension:

Conventional pharmaceutical excipients are used and they all comply with the relevant Ph. Eur. monographs, except the artificial vanilla flavour and the cation exchange resin (which are not the subject of any pharmacopoeial monographs and are therefore the subject of in house monographs). Typical certificates of analysis are presented for each excipient and these demonstrate their compliance with the stated specifications.

The qualitative composition of the artificial vanilla flavour and the quality specifications for the propylene glycol carrier (solvent) have been provided and are acceptable to control its quality. The in-house specification for it includes the following quality characteristics: odour, taste, identity, clarity, colour and relative density, and is suitable to control this excipient. The test methods are described. Batch analysis data are in agreement with the stated quality specifications. Additionally the manufacturer has confirmed that vanilla flavour complies with the requirements of Council Directive 88/388/EEC as amended.

Amberlite IRP 64 is an unifunctional linked carboxylic cation exchange resin prepared from methacrylic acid and divinylbenzene which is not described in any pharmacopoeia, although the potassium form is the subject of a USP monograph. Therefore, an in-house specification is used which is suitable and contains the following quality characteristics: appearance, colour, identity, sodium content, methacrylic acid content, water extractable content, loss on drying, particle distribution, heavy metals, microbial purity and assay. The test methods are described. Batch analysis data are in agreement with the stated quality specifications.

Packaging

Tablets:

The primary packaging for the tablets is blister strips consisting of a polyamide/aluminium/ polypropylene bottom foil and an aluminium foil with a heat-seal coating (top foil). The heat-seal lacquer is fully described. The polypropylene used is in agreement with the requirements of the Ph. Eur. and the heat-seal lacquer and polypropylene used in the bottom foil both meet appropriate specifications. For both of the foils, specifications for routine tests are provided. Likewise for the pure

aluminium foil. Batch analysis data for the top and bottom foils are in agreement with the stated specifications.

Oral Suspension:

Veraflox Oral Suspension is presented in white, polyethylene bottles closed by a polypropylene child-resistant screw cap with tamper-evident ring and with a polyethylene adapter (injection moulding plug). The 15 ml size is supplied with a 3.0 ml polypropylene syringe (graduated up to 2.0 ml in 0.1 ml steps). No administration syringe is included with the 30 ml pack size.

The containers, closures and syringes all comply with the requirements of the European Pharmacopoeia monograph 3.1.3 "Polyolefines" and the monograph 3.2.2 "Plastic containers and closures for pharmaceutical use". Declarations are presented which demonstrate that all materials used, including the raw material used for the production of the silicone ring of the syringe, are in compliance with the relevant European and FDA requirements. Specifications for routine tests are also provided for the bottle, the screw cap and the syringe. Batch analysis data demonstrate compliance with the stated specifications. The graduations on the printed scale of the syringe are checked and the results comply with requirements of the Ph. Eur. monograph 2.9.27 "Uniformity of mass of delivered doses from multidose containers".

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Tablets:

Lactose monohydrate is pharmaceutical grade, its TSE risk is negligible and can therefore be excluded from the scope of the TSE Guideline (EMEA/410/01- Rev.2). Artificial beef flavour is obtained from human grade pork liver and contains no beef or bovine products. Veraflox Tablets are in compliance with the Ph. Eur. monograph 5.2.8. "Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" and there is no risk of transmission of spongiform encephalopathy from their use. The starting materials of animal origin used in the production of the tablets comply with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Commission Directive 1999/104/EEC.

Oral Suspension:

The active substance and all excipients used in the manufacture of Veraflox 25 mg/ml Oral Suspension are in accordance with the Ph. Eur. monograph 5.2.8. "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products". The starting materials of animal origin used in the production of the oral suspension comply with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Commission Directive 1999/104/EEC.

Control tests during production

Not applicable.

Control tests on the finished product

Tablets:

All strengths of Veraflox Tablets are tested to specifications which include tests, by suitable and validated methods, for appearance, identification of the active substance, uniformity of dosage units, microbial quality, assay, degradation products, dissolution and moisture content. Degradation products

are also controlled, and the limits applied are justified by reference to stability studies and toxicology studies and in accordance with the relevant VICH guideline ('Impurities in new veterinary medicinal products'). The manufacturing process and storage were shown to have no influence on enantiomeric/diastereomeric purity of the pradofloxacin. No routine test at release is therefore necessary. The limits applied to each of the specifications for the finished product are demonstrated to be appropriate to control the quality of the finished product for its intended purpose. Batch analysis data from pilot-scale and production batches of each tablet strength confirm satisfactory uniformity of the product at release.

Oral Suspension:

Veraflox 25 mg/ml Oral Suspension is tested to a specification which includes tests, by suitable and validated methods, for appearance, identification of the active substance and sorbic acid, relative density, viscosity, pH, microbial quality, assay of pradofloxacin, assay of sorbic acid, degradation products and dissolution. The specified tolerance ranges for pradofloxacin assay and sorbic acid assay at release are in line with the relevant EU and VICH guidelines. The proposed limits are justified. The absence of a test and limits for resuspendibility are justified as the product failed to show any sedimentation, even after 12 months storage at room temperature. Analysis certificates are presented for three pilot batches. All results are in accordance with the specifications and show batch to batch uniformity.

Stability

Tablets:

The shelf life specifications are the same as the release specifications except for the upper limit for water content, which was widened slightly at end of shelf life. Testing methods for stability studies are the same as those described for release.

Stability studies demonstrated that Veraflox Tablets are stable in their aluminium blisters for up to 60 months at 25°C/60%RH and 30°C/70%RH, and for up to 6 months at 40°C/75%RH. The results are in accordance with the stated specifications. Stability of tablets in the proposed bulk containers up to the claimed storage period was also demonstrated.

Pradofloxacin is sensitive to light (discoloration on the surface, but no degradation) and in a mixture with tablet excipients this effect is reduced, but still observable. As the tablets are packaged in aluminium blisters (which offer total protection against light) the absence of photostability studies on the finished product was justified. With the stability data provided, the proposed shelf-life of 3 years with no restrictions on storage is justified when tablets are stored in the commercial packaging (aluminium blisters).

The posology dictates that half tablets can be used. The stability of half tablets (15 and 120 mg) at ambient conditions outside their sealed blister packs was investigated up to three days, and their stability was demonstrated up to this time. Therefore, a half tablet may be stored (in the opened blister – see the package leaflet for instructions) for one day after the blister has been opened.

Oral Suspension:

The stability of the bulk suspension has been demonstrated and the proposed maximum standing time justified.

Quality specifications for the oral suspension at end of shelf life are the same as for the release specification, except for the limits for pradofloxacin and sorbic acid which were widened for shelf-life purposes. Testing methods for stability studies are identical to those described for release. In addition

to the specified parameters, preservative efficacy (Ph. Eur.), viscosity and loss of mass were also demonstrated in the stability studies.

Stability studies on pilot and production scale batches of the oral suspension, after up to 60 months storage at both 25°C/60%RH and 30°C/70%RH, and for 6 months at 40°C/75%RH showed the product to be stable in the proposed packaging. Photostability testing was performed on two batches according to the current VICH guideline. The unprotected samples in the original bottles showed no significant changes in colour or pradofloxacin assay, and although the content of degradation products increased they remained within the limits. Therefore, no special protection from light and no special labelling were considered necessary. Considering all the stability data provided, the proposed shelf-life of 3 years, with no restrictions on storage is justified.

In-use stability data justify the proposed in-use shelf-life of 3 months. The appropriate preservative efficacy has been proven on aged batches.

Overall conclusions on quality

Veraflox is presented as 15 mg, 60 mg and 120 mg tablets for use in dogs and cats, and also as a 25 mg/ml oral suspension for use in cats.

Pradofloxacin, a fluoroquinolone carboxylic acid, has been developed as an antibacterial for use in veterinary medicine. Out of four possible isomeric forms the S,S-configuration has been chosen because of its high antibacterial activity. Pradofloxacin crystallizes in six modifications. Production of the chosen modification is controlled during release of the drug substance, and this form is stable under normal storage conditions and has been found to be most suitable for both the tablets and the oral suspension.

The flavour used in the tablets originates from pig livers and is irradiated to ensure inactivation of any potential contaminant viruses and microorganisms. Given the specified source and processing details of the pig livers used and the subsequent heat treatment of the pork liver powder during the manufacture of this flavour, the risk of viral contamination is concluded to be negligible.

The control tests for both of the finished products cover the relevant quality criteria and are suited to confirm adequate and consistent product quality.

Stability data for the active substance, pradofloxacin, are available for up to 36 months stored at 25°C/60% RH and 40°C/75% RH (18 months of accelerated conditions have been tested). Additional data from earlier and follow up stability studies support the claimed retest period.

The tablets have been stored at long term storage conditions (25°C/60% RH) and at accelerated conditions (30°C/70% RH and 40°C/75% RH) for up to 60 months. It is necessary to use aluminium blisters as the primary packaging material in order to prevent moisture uptake by the tablets. A shelf life for the tablets of 3 years, with no restrictions on storage conditions, is justified.

Three batches of each container size of the oral suspension have been stored at 25°C/60% RH and at accelerated conditions (30°C/40% RH, 30°C/70% RH and 40°C/75% RH) up to 60 months. Additional stability data are available and support the claimed shelf-life of 36 months with no restrictions on storage conditions.

In-use stability data were provided and also appropriate preservative efficacy data, which together justify the in-use shelf-life of 3 months.

3. Safety assessment

Pharmacodynamics

For the mode of action and antimicrobial activity see section 4.

Secondary pharmacodynamic effects

The potential secondary pharmacodynamic and toxic effects have been investigated in a series of preclinical safety studies, including pharmacological *in vitro* and *in vivo* studies in laboratory animals and the target animal species, respectively. Pradofloxacin had no effects on behaviour, motility, nociception, body temperature or hexobarbital-induced anaesthesia and no specific effects on gastrointestinal function in these tests. Pradofloxacin did not induce contractions or relaxation of isolated Guinea pig ileum and the effects of acetylcholine, histamine, and barium were not influenced by it. At doses of 10 and 30 mg/kg bodyweight it had no pro-convulsive potential *in vivo* after oral or intravenous administration to rats. In a mechanistic model using extracellular recordings from rat hippocampus slices, pradofloxacin exhibited a moderate excitatory potential which was comparable to that of moxifloxacin.

A trend for diuretic effects was seen after oral application to rats starting at a dose rate of 3 mg/kg bw, with significantly increased urine volumes being noted after 10 and 30 mg/kg bw. This effect was accompanied by an increased potassium excretion starting at a dose rate of 30 mg/kg bw.

Intravenous cumulative doses of 3, 10 and 30 mg/kg bw in anaesthetised dogs led to changes of heart rate, peripheral resistance at the two higher doses, and at 30 mg/kg bw to increased inspiratory pressure and pulmonary resistance, which were interpreted as a consequence of a pseudoallergic reaction. A dose dependent, small to pronounced prolongation of QTc-interval and an increase of T-wave height was seen in this study at both higher cumulative doses.

Pharmacokinetics

A number of GLP compliant studies were performed to investigate the pharmacokinetics of pradofloxacin, including the metabolism of radiolabelled pradofloxacin in rats. In dogs and cats, the pharmacokinetics of pradofloxacin (in the final formulations, i.e., tablets and oral suspension) have been sufficiently characterised. No gender-related differences in the pharmacokinetic behaviour of pradofloxacin have been reported.

Absorption

Pharmacokinetic investigations in rats showed that pradofloxacin was rapidly absorbed and distributed throughout all compartments of the body.

In dogs, pradofloxacin is rapidly (T_{max} of 2 hours) absorbed after oral administration of the therapeutic dose reaching peak concentrations of 1.6 mg/l. The oral tablets show high bioavailability irrespective of the tablet strength or dose administered. It was shown that the pradofloxacin concentrations increase linearly with increases in the administered dose. Repeated dosing resulted in no impact on the pharmacokinetic profile (accumulation index 1.1).

In cats, pradofloxacin is rapidly absorbed after oral therapeutic doses, reaching peak concentrations of 1.2 mg/l within 0.5 hours (tablets) and 2.1 mg/l within 1 hour (oral suspension). The bioavailability was shown to be at least 60% (oral suspension) and close to 70% (tablets). As in the dog, in cats pradofloxacin concentrations increased linearly with increasing dose, and repeated dosing resulted in

no impact on the pharmacokinetic profile (accumulation index 1.0 for the tablets and 1.2 for the oral suspension).

(Plasma/Tissue) Distribution

In dogs, the volume of distribution (Vd) is high (> 2 l/kg bodyweight), indicating good tissue penetration. Pradofloxacin concentrations in skin homogenates of dogs exceed those in serum by up to 7 times. *In vitro* plasma protein binding is moderate (35%) and within the range known for other fluoroquinolones.

In cats, the volume of distribution (Vd) is similarly high, > 4 l/kg bodyweight (tablets) and >1 l/kg bodyweight (oral suspension), indicating good tissue penetration. *In vitro* plasma protein binding is moderate (30%).

Metabolism

In vitro studies on hepatocytes of the rat, cat and dog, pig (female), cattle (female) and man were provided. The results indicate that glucuronidation and sulfation are the major biotransformation pathways of pradofloxacin in all species. Pradofloxacin is conjugated with glucuronic acid in significant amounts in cats (up to 50%). In canine hepatocytes, in addition to glucuronides, only negligible amounts of mono- and bishydroxylation products were detected. In female Wistar rats, sulfation was by far more pronounced and proved to be the major metabolic pathway.

Excretion

In rats, excretion of pradofloxacin occurred by the biliary and extrabiliary routes into the stomach and intestines. Pradofloxacin was excreted mainly as the parent compound. The sulfate was the only metabolite found in rats.

In dogs, approximately 40% of pradofloxacin administered orally or intravenously is excreted via the urine, independent of the dose or route of administration. Renal excretion is rapid, with approximately 85% of the fraction of pradofloxacin recovered in urine being excreted within 24 hours after administration. Pradofloxacin is cleared from the body at 0.24 l/h/kg. Unchanged pradofloxacin and glucuronide are the main excretion products. The plasma elimination half-life in dogs averages 8 hours.

In cats, approximately 10% of the administered drug is excreted via the kidneys. Renal excretion is rapid with approximately 70% of the fraction recovered in urine being excreted within 24 hours after administration. Pradofloxacin is cleared from the body at 0.27 l/h/kg. Unchanged pradofloxacin and glucuronide are the major excretion products. The plasma elimination half-life in cats averages in excess of 8 hours (tablets) and 7 hours (oral suspension).

Toxicology

Single dose toxicity

Acute toxicity studies of pradofloxacin were carried out in male and female rats and mice. Pradofloxacin is of low to moderate acute toxicity. The active substance was administered orally or intraperitoneally. The studies were conducted in compliance with GLP and according to the OECD guidelines for acute oral toxicity (No 401 and 423). The LD_{50} in rats and mice after a single oral application was 1000-2000 mg/kg bw and 500-1000 mg/kg bw, respectively. In rats, reversible effects on the kidney were seen with 100 and 500 mg pradofloxacin/kg bw. Cytotoxic effects have been observed in the testes and epididymides, which were reversible at 500 mg/kg bw and irreversible at 1000 mg/kg bw. The haematopoietic and lymphoid systems were also affected, but recovered after the withdrawal of pradofloxacin. Although pradofloxacin showed cytotoxic effects on the kidney, testes,

haematopoietic and lymphoid systems, and the liver in sublethal doses, the doses used were far above the relevant therapeutic doses.

The approximate LD_{50} after a single intraperitoneal application in rats was >50 mg/kg bw. Clinical signs and various macroscopic findings on liver, kidney, gastrointestinal tract, spleen, testes and inflammation in the abdominal cavity were seen at 100 mg/kg bw. An acute dermal toxicity study in the rats showed an LD_{50} of >2000 mg/kg bw.

Various toxicity studies (acute oral and dermal toxicity, dermal and eye irritation and dermal sensitisation studies) were performed in laboratory animals. Administration of the final oral suspension formulation at an oral dose of 2 ml (corresponding to approximately 50 mg/kg bw) and at a dermal dose of 4 ml (corresponding to approximately 100 mg/kg bw) was not acutely toxic to rats. Veraflox 25 mg/ml Oral Suspension for Cats had no eye or skin irritating potential and was not sensitizing.

In young cats, pradofloxacin proved to be well tolerated after a single oral dose of 100 mg/kg bw.

In dogs, one oral single dose of 100 mg pradofloxacin /kg bw did not adversely affect renal function. However, in one individual animal there was evidence of transient overloading of its renal excretory capacity.

Repeat dose toxicity

In rats and mice, repeat dose studies were performed in the form of feeding studies, with up to 7000 to 7500 ppm pradofloxacin (corresponding to <999 mg/kg bw in rats and <2675 mg/kg bw in mice) being administered for up to 4 and 13-14 weeks, with or without following recovery periods. Several special tests were included in individual rat studies as measurements of liver tissue enzyme activity, immunotoxicity and kidney cell proliferation. Toxicokinetic investigations in rat feeding studies showed stable and dose proportional plasma levels with no indication of either accumulation or increased metabolism and elimination.

Prominent features of drug effects at low doses in these studies were diarrhoea, partly leading to dehydration of the animal, increased water intake, haematological alterations such as decreased neutrophil and macrophage counts, changes in antibody titres, urinary volume and density, decreased liver enzyme activities, changes in thymus weights and enlarged caeca. At higher doses, degenerative and inflammatory effects in the intestinal tract were seen, as well as changes in the cartilage of knee joints in individual animals. While in the subacute studies, No Observed Effect Levels (NOELs) could be allocated as 500 ppm in rats and 100 ppm in mice, corresponding to about 45-50 and 30-35 mg/kg bw respectively, the subchronic toxicity studies did not reveal reliable NOELs and the lowest doses in rats (approximately 25 mg/kg bw) at best could be designated as Low Observed Effect Levels (LOELs). In mice, the lowest dose of approximately 150 mg/kg bw was a clear effect level, at which caecal distension, increased water and feed intake, and decreased thymus weights could be observed.

Two additional repeated dose toxicity studies have been performed, a 13 week and a 52 week oral feeding study in the rat with additional toxicokinetic investigations. From the 13 week study no NOEL could be established, and from the 52 week study a NOEL of 250 ppm, corresponding to 12.5/17.0 mg/kg bw for males and females respectively, could be established.

In young adult or growing dogs of less than 6 months, two 2-week oral repeat dose toxicity studies (up to 44 mg/kg bw) and a 13-week oral repeat dose toxicity study (up to 15 mg/kg bw) were performed. In young growing dogs, the administration of pradofloxacin at 4 mg/kg bw per day and above induced articular cartilage lesions, however these are well known effects of quinolones. No other toxic effects were observed. In particular, no changes in potential target organs and tissues including cardiac function, blood pressure, liver, kidneys, bone marrow, male reproductive organs and eyes were observed. Increased absolute and relative liver weights were found at daily doses of 19 mg/kg bw, and

above, but no histopathological correlates or changes in liver tissue enzyme activities were found. Thus, from a toxicological point of view, a NOEL of 4 mg/kg bw was derived. From pathological point of view, no NOEL could however be established. Appropriate information is included in the "Contraindications" parts of the SPC (section 4.3) and Package Leaflet (section 5), addressing both the risk of quinolone-induced chondropathy in growing dogs and a contraindication for using pradofloxacin in animals with persisting joint lesions (as lesions may worsen during therapy).

Reproductive toxicity

In addition to a rat one-generation study, a complete data package of well-conducted studies assessing the reproductive and developmental toxicity has also been provided. This comprises a rat two-generation study, an abstract of a rat embryo-foetal pilot study and a complete rat embryo-foetal study, and two rabbit developmental toxicity studies.

In the rat two-generation study, the following No Observed Adverse Effect Levels (NOAELs) were established: 600 ppm in the feed for parental and offspring toxicity and 120 ppm for parental reproductive parameters. These figures correspond to about 60 mg/kg bw/d for parental toxicity, about 40 mg/kg bw/d for offspring toxicity and about 8 mg/kg bw for parental reproductive parameters. Toxicity was mainly derived from typical antibiotic overdose effects such as gastrointestinal disturbances. This was accompanied by decreased litter sizes and pup weights which are considered secondary effects.

In the pivotal rat embryo-foetal study, the following No Observed Adverse Effect levels were established: 5 mg/kg bw/day for maternal toxicity and foetal toxicity. Maternal toxicity also mainly derived from gastrointestinal disturbances. In the offspring, an increased incidence of ocular malformations was apparent at 35 mg/kg bw/day (LOAEL) which was interpreted as possible direct cytotoxic effect.

From the two rabbit studies a NOAEL of 1 mg/kg bodyweight/day for parental reproductive parameters was derived. Pradofloxacin led to severe gastrointestinal effects and abortions, which is not surprising for an oral antibiotic in this species. Foetal toxicity was established with a NOAEL of 3 or 4 mg/kg bw/d, respectively. This was based on reduced foetal weight, delayed ossification and ocular malformations in the higher dose groups.

As a result of these findings, use of the product in pregnant or lactating animals is contraindicated and appropriate statements are included in the product literature (SPC sections 4.3 and 4.7, and Package Leaflet sections 5 and 11). For breeding animals, treatment is considered to be without risk.

Genotoxicity

Data were provided from a comprehensive battery of genotoxicity assays, including tests for gene mutations and chromosomal aberrations *in vitro* and *in vivo*.

In vitro data:

Pradofloxacin induced mutations in the Ames test in *Salmonella typhimurium* strain TA102 but not in the other strains. It induced chromosomal aberrations in cultured Chinese hamster V79 cells in both the absence and presence of S9 and exhibited photoclastogenic properties in V79 cells. Finally, the substance produced mutations in the HPRT assay in Chinese hamster V79 cells.

A comparison of the *in vitro* genotoxicity of a number of fluoroquinolone compounds versus the Low Observed Effect Concentrations (LOECs) at which these compounds induced topoisomerase II inhibition in cultured cells (six fluoroquinolones were investigated for their effects on stabilisation of the TOPO IIα-DNA complex) demonstrated the absence of *in vitro* genotoxicity at doses that do not cause topoisomerase II inhibition. The correlation coefficient between the LOECs for topoisomerase II

inhibition (molar) and *in vitro* genotoxicity strongly indicates a causal relation between inhibitory potency on topoisomerase II and genotoxicity. The absence of genotoxicity at doses that do not cause topoisomerase II inhibition demonstrates that this is a threshold related mode of genotoxic action. This supports the conclusion that the positive *in vitro* genotoxicity effects for pradofloxacin were directly correlated with topoisomerase II inhibition and that a threshold therefore exists for the observed *in vitro* genotoxicity.

In vivo data:

Pradofloxacin was evaluated in several *in vivo* mutagenicity studies. These studies comprised the dominant lethal tests in mice, bone marrow micronucleus investigations in mice and rats, an unscheduled DNA synthesis study in rats, a photo comet assay in mice, ^{32}P-postlabelling studies in mice, and a micronucleus study in the target animal species, the dog, using repeated oral dosing for up to 35 days with 3.3 times the recommended therapeutic dose.

Pradofloxacin was negative in the dominant-lethal-test and the unscheduled DNA synthesis test. It was also negative in the photo-comet assay in mice at doses of up to 200 mg/kg. In a ^{32}P-postlabelling assay, no ^{32}P-labelled adducts were found in mouse bone marrow or liver either after a single oral dose of 640 mg/kg or 7 daily oral doses of 320 mg/kg/day.

In four *in vivo* micronucleus tests (2 studies in mice; 2 studies in rats) pradofloxacin induced micronuclei in the bone marrow of both rats and mice at non-cytotoxic dose levels. The NOELs were 200 mg/kg bodyweight (rats) corresponding to an average maximum plasma concentration of 9.9 µg/ml (AUC 58.5 µg.h/ml) and 160 mg/kg bodyweight (mice) corresponding to an average maximum plasma concentration of 9.5 µg/ml (AUC 25.6 µg.h/ml) respectively.

Based on the dose, pradofloxacin was observed to be a more potent inducer of micronuclei *in vivo* than other fluoroquinolones. The Committee considered the systemic exposure to be the most appropriate dose parameter for the comparison of the potency of pradofloxacin with other fluoroquinolones. When plasma drug levels were considered, the systemic exposure to pradofloxacin and another fluoroquinolone were shown to be similar at doses leading to micronucleus induction.

In dogs, young reticulocytes in peripheral blood and bone marrow cells were assessed for micronuclei using flow cytometry, after daily doses of 15 mg/kg bodyweight for a period of 35 days. There were no statistical differences in micronucleus frequencies between treated and control groups at any sample time. There is therefore no evidence of a positive response in this study at doses corresponding to 3.3 X the recommended maximum dose in dogs. A NOEL (15 mg/kg) for micronuclei induction was thus demonstrated in the dog where the peak plasma concentration was 5.19 µg/ml and AUC was 37.75 µg.h per ml (2.1 – 2.6 times higher than the expected systemic exposure at the maximum therapeutic dose of 4.5 mg/kg/day).

Overall conclusion on genotoxicity:

The overall pattern of genotoxicity of pradofloxacin is consistent with other fluoroquinolone topoisomerase II inhibitors. The genotoxicity of pradofloxacin is threshold related and therefore margins of safety (MOS) assessments can be performed.

Carcinogenicity

Pradofloxacin was evaluated for carcinogenic potential in mice and rats.

The dietary carcinogenicity study in rats is considered to be of limited value for the assessment of the carcinogenicity of pradofloxacin in rats because (1) the survival rate in both the male control group and the highest level dose group was too low to allow conclusions to be drawn, and (2) even the

highest dose level did not elicit any signs of toxicity. Thus the requirements of OECD 451 were not met.

The carcinogenicity study in the mouse was undertaken in mice fed diets containing 0, 150 ppm, 500 ppm, 2000 ppm or 7000 ppm for 19 months. An increase in the incidence of gall bladder adenoma in females was observed only at the highest dose level which was reported to exceed the historical control incidence. Concurrent gall bladder dilation was reported along with an increased incidence of mucosal hyperplasia at both 2000 ppm (males) and 7000 ppm (males and females). Concretions were reported at 7000 ppm in both sexes. Consequently, the highest dose level of 7000 ppm is regarded as a LOAEL for tumourigenicity. Hyperplasia of the gall bladder (mouse) or intrahepatic bile ducts (rat) was also reported in toxicity studies of ≥1 year duration. These data suggest a tumourigenic response secondary to mucosal hyperplasia. The Committee agreed that the possibility of topoisomerase inhibition being involved in the mode of carcinogenic action cannot be entirely excluded, and considered the tumourigenic effect to be mediated by a threshold based mode of action.

Margins of safety (MOS)

Genotoxicity and carcinogenicity were considered to be the most critical endpoints for the safety assessment. MOS were determined for both endpoints for the target species, dogs and cats, and for users administering the products (see below). The Committee believed that the most relevant study for the risk assessment of pradofloxacin was the carcinogenicity study.

MOS Genotoxicity - target species:

The most relevant study to assess MOS for genotoxic effects in dogs is the micronucleus test (MNT) in dogs with an established NOAEL of 15 mg/kg bodyweight/day (the highest dose tested). It is noted that as no genotoxicity was seen in the dog study, the true no effect level is likely to be higher. The MOS determined using AUC data is 2.6. Given that mutagenicity data have been provided in the target species dog, and it is likely that the MOS is higher, these data suggest an acceptable MOS in use regarding genotoxicity in the dog.

The most relevant genotoxicity study to assess MOS for genotoxic effects in cats is the mouse micronucleus study, in which the NOEL was 160 mg/kg bodyweight (no data in the target species are available). The MOS, based on the AUC determination for the cat tablet, is 3.0, and 2.1 for the oral suspension. It is noted that the MOS for the cat (tablet) calculated from the different *in vivo* genotoxicity studies range from 3.0 – 6.9, and for the cat (suspension) from 2.1 – 4.7. Furthermore, the data suggest there is limited inter-species variation in sensitivity regarding *in vivo* genotoxicity. Overall it can be concluded that there are acceptable MOSs regarding genotoxicity.

MOS Carcinogenicity – target species:

A MOS assessment based on comparison of cumulative exposure (AUC x treatment days in the mouse carcinogenicity) compared to cumulative exposure in the target species (AUC x treatment days in target species) was undertaken. The Committee decided this approach is justified as the tumourigenic effect was observed only after long-term exposure (19 months).

With regard to the dog, a MOS of 125 was reported using a dose level of 7000 ppm. This is a MOS based on systemic exposure and is considered acceptable even if 7000 ppm is regarded as a LOAEL and not a NOAEL. The calculated MOS using the AUC at 2000 ppm (i.e. the NOAEL) is 40. The Committee also considered this MOS to be acceptable.

With regard to the cat, a MOS of 1073 for the 15 mg tablets, and a MOS of 740 for the suspension, were calculated using a dose level of 7000 ppm. These MOSs are based on systemic exposure and are considered acceptable even if 7000 ppm is regarded as a LOAEL and not a NOAEL. The calculated MOS

using the AUC at 2000 ppm (i.e. at the NOAEL) is 343 for the tablet and 237 for the suspension. The Committee considered these MOSs to be acceptable.

Studies of other effects

Some additional studies investigating other effects, which are relevant to the safety evaluation of pradofloxacin were presented. These studies provided further information concerning the CNS-, as well as the photo-, chondro- and immunotoxicity of the compound.

Cytotoxicity/Phototoxicity

Some fluoroquinolones are known to be phototoxic, photoallergic or photomutagenic, therefore, the phototoxic and photoallergic effects of pradofloxacin were tested. The cytotoxicity of various fluoroquinolones, including pradofloxacin, was tested in three cell lines: human lymphoblastoma cells from bone marrow (IM9), mouse macrophage cells (J774.A1) and rat hepatoma cells (H4-II-E-C3). Pradofloxacin was shown to possess a pronounced cytotoxic potential *in vitro* in comparison to other fluoroquinolones.

The phototoxic potential of pradofloxacin was determined in a 3T3 cell line. Pradofloxacin was classified as moderately phototoxic *in vitro*.

The photoallergic potential of pradofloxacin after oral administration was tested in the local lymph node assay of mice and guinea pigs. Pradofloxacin has a moderate photoreactive potential in guinea pigs and a low photoreactive potency in mice.

Skin/eye irritation

Dermal and eye irritation and dermal sensitisation were studied with the final formulation Veraflox 25 mg/ml Oral Suspension for Cats in rabbits and guinea pigs respectively. Pradofloxacin has no skin or eye irritation or sensitisation potential.

Immunotoxicity

No conspicuous immunotoxic reactions were seen at pradofloxacin levels comparable to the intended therapeutic doses.

Chondrotoxicity

Pradofloxacin showed strong chondrotoxic effects *in vitro* on canine chondrocytes. At repeat oral doses of 4 mg/kg and above, the typical quinolone-induced joint lesions were evident (as shown in the repeat dose toxicity studies on young Beagle dogs at the age of up to six months). The risk of quinolone-induced chondropathy is therefore addressed in both the SPC and Package Leaflet.

Studies on other substances in the formulations

Data from various studies assessing the toxicological properties of propylene glycol, Amberlite IRP 64, ascorbic acid (E 300), sorbic acid (E200), Xanthan gum and vanillin flavour (artificial) were provided. The CVMP agreed that the use of these substances in Veraflox products would be safe for cats and dogs and also for users.

User safety

Veraflox is a veterinary medicinal product containing pradofloxacin for use in dogs and cats and is available as tablets or as an oral suspension. The acute oral toxicity of the product is very low, and pradofloxacin was considered non-irritating to the eyes and skin, and has no potential for skin

sensitization in a guinea pig maximization test according to Magnusson and Kligman. Pradofloxacin did not induce foetotoxic or teratogenic effects at doses below maternal toxicity. For ocular malformations occurring at maternotoxic doses a direct toxic effect during organogenesis could not be ruled out. Pradofloxacin has been shown to have a moderate photoreactive potential in guinea pigs and a low photoreactive potency in mice. However, it is highly unlikely to be a risk for users because of the low exposure that would result from accidental contact. Pradofloxacin was shown to be genotoxic *in vitro* and *in vivo* with an underlying threshold-based mechanism. A high dose tumourigenic effect in the mouse (gall bladder adenoma) following long term administration was due to a threshold-related mode of action.

The excipients are recognised as safe by the CVMP for the target animals and users.

Margin of safety (MOS), User

MOS Genotoxicity:

Two possible risk assessment scenarios were identified, namely dermal exposure of a user to the suspension, and inadvertent exposure of a child through oral ingestion of a tablet or suspension. The calculated dose following dermal exposure to the suspension is 0.0083 mg/kg bodyweight, which provides a MOS of 1800 compared to the NOAEL reported (15 mg/kg bodyweight/day) in the micronucleus study in dogs. This MOS assessment is considered to be acceptable.

The inadvertent oral ingestion of a complete syringe would give rise to an oral dose of 7.5 mg/kg bodyweight for a 10 kg child. The MOS based on the NOAEL for the mouse MNT is 21. The dose resulting from oral ingestion of a tablet for a 10 kg child was 12 mg/kg bodyweight. The MOS based on the NOAEL for the mouse single dose MNT is 13. There is practically no MOS in relation to the MNT in dogs for this scenario which justifies very restrictive precautionary measures for children.

MOS Carcinogenicity:

The exposure patterns identified in the two exposure scenarios are acute exposures, while the carcinogenic effects identified in the mouse are due to chronic exposure for 19 months, and consequently the risk of carcinogenicity for adults and children is considered to be negligible.

However, in order to avoid unnecessary exposure, several warning phrases were included under section 4.5 of the SPC for Veraflox 25 mg/ml Oral Suspension and Veraflox Tablets (and in the package leaflets). The Committee was satisfied that the following user safety information in the product literature was adequate and appropriate.

For Veraflox 25 mg/ml Oral Suspension:

- Due to potential harmful effects, the bottles and the filled syringes must be kept out of the reach and sight of children.
- People with known hypersensitivity to quinolones should avoid any contact with the veterinary medicinal product.
- Avoid skin and eye contact with the veterinary medicinal product. Wash hands after use.
- In case of accidental contact with the eyes, wash immediately with water.
- In case of contact with the skin, rinse off with water.
- Do not eat, drink or smoke while handling the veterinary medicinal product.
- In case of accidental ingestion, seek medical advice and show the package leaflet or the label to the physician.

For Veraflox Tablets:

- Due to potential harmful effects, the tablets must be kept out of the reach and sight of children.

- People with known hypersensitivity to quinolones should avoid any contact with the veterinary medicinal product.
- Avoid skin and eye contact with the veterinary medicinal product. Wash hands after use.
- Do not eat, drink or smoke while handling the veterinary medicinal product.
- In case of accidental ingestion, seek medical advice and show the package leaflet or the label to the physician.

Resistance development in human medicine

Pradofloxacin is not used in human medicine.

Environmental safety

Veraflox Tablets and Oral Suspension are for use in companion animals for individual animal treatment only. Thus, the use of the product is not expected to pose a risk for the environment. In line with VICH-GL 6 the environmental risk assessment stops in phase I.

Overall conclusions on safety

Veraflox is a veterinary medicinal product containing pradofloxacin indicated for use in dogs and cats and is available as tablets and also as an oral suspension. The acute oral toxicity of the product is very low. Repeat dose toxicity studies were conducted in rats, mice and dogs. Prominent features of drug effects at low doses in these studies were diarrhoea, partly leading to dehydration of the animal, increased water intake, haematological alterations such as decreased neutrophil and macrophage counts, changes in antibody titres, urinary volume and density, decreased liver enzyme activities, changes in thymus weights and enlarged caeca. At higher doses, degenerative and inflammatory effects in the intestinal tract were seen, as well as changes in the cartilage of knee joints in individual animals. The risk of quinolone-induced chondropathy in growing dogs, and a contraindication for the use of pradofloxacin in animals with persisting joint lesions, are addressed in the SPC and Package Leaflet accordingly.

Pradofloxacin was considered non-irritating to the eyes or on the skin and to have no potential to induce skin sensitisation in a guinea pig maximisation test.

Pradofloxacin did not induce foetotoxic or teratogenic effects at doses below those at which maternal toxicity occurred. For ocular malformations occurring at maternotoxic doses a direct toxic effect during organogenesis could not be ruled out.

The overall pattern of genotoxicity of pradofloxacin is consistent with other fluoroquinolone topoisomerase II inhibitors. The genotoxicity of pradofloxacin is threshold related and margin of safety (MOS) assessments can therefore be undertaken. The AUC, where available, is the appropriate parameter to use in MOS assessments.

Carcinogenicity studies were performed in rats and mice. No final conclusions could be drawn from the rat study due to major shortcomings. In the mouse carcinogenicity study, a high dose tumourigenic effect (gall bladder adenoma) was observed at a dose of 7000 ppm and is considered to be due to the threshold related mode of action. With regard to the target species, dogs and cats, acceptable MOSs could be calculated. These MOSs indicate that a carcinogenic risk associated with the therapeutic use of this product is negligible.

A user safety assessment has been provided which shows that dermal exposure is considered the most likely route of exposure for a person administering the product to animals. For small children (10 kg bw) accidental ingestion of Veraflox Tablets or Veraflox Oral Suspension could be harmful. In

addition to precautionary measures provided by the packaging (child resistant closure of the bottle and the blister packaging used for the tablets), appropriate warnings are included in the SPCs and Package Leaflets to enhance the safety for the user, and in particular also against the accidental exposure of small children.

4. Efficacy assessment

Pharmacodynamics

Mode of action

Pradofloxacin is a novel third generation fluoroquinolone which exerts bactericidal activity. It shows a wider spectrum of activity against Gram-positive and anaerobic bacteria compared to other veterinary fluoroquinolones. Its primary mode of action involves interaction with enzymes essential for major DNA functions like replication, transcription and recombination. The primary targets for pradofloxacin are the bacterial DNA gyrase and topoisomerase IV enzymes. Reversible association between pradofloxacin and DNA gyrase or DNA topoisomerase IV in the target bacteria results in inhibition of these enzymes and death of the bacterial cell.

Antibacterial spectrum

A number of studies were presented demonstrating the *in vitro* activity of pradofloxacin towards pathogens isolated from canine and feline wound infections and abscesses, canine pyoderma, canine periodontal infections, canine urinary tract infections, and feline upper respiratory tract infections. The isolates were tested according to standardised Clinical and Laboratory Standards Institute (CLSI) methodology. The strains examined came from a number of different European countries and were considered representative of the European region. As the MICs of both the facultative anaerobic/aerobic pathogens (*Staphylococcus intermedius*[1], *Pasteurella multocida*, *Escherichia coli*) and the anaerobic pathogens (*Prevotella* spp*.* and *Porphyromonas* spp*.*) are consistent between two different sampling periods used (2001-2003 and 2004-2007) it was justified for the two data sets to be pooled. The resulting large data set (2001-2007) comprises over 1200 strains of *S. intermedius*, and over 300 strains each of *E. coli*, *P. multocida*, *Porphyromonas* spp*.* and *Prevotella* spp. The more recent MIC data confirm that good susceptibility of the claimed target pathogens to pradofloxacin.

Bacterial kill kinetic studies, which included facultative anaerobic/aerobic and anaerobic bacteria, demonstrated that pradofloxacin exhibits a concentration-dependent bactericidal activity. This was confirmed in a study in which pradofloxacin showed bactericidal activity at concentrations below 0.5 µg/ml against the target pathogens *S. intermedius*, *E. coli*, *P. multocida*, *Porphyromonas* spp*.* and *Prevotella* spp*.*

Clear post-antibiotic effects were demonstrated for the claimed target bacteria and confirmed in another study in anaerobic pathogens (*Prevotella* spp*., Porphyromonas* spp*.*). Results of studies on the possible influence of environmental factors on the antimicrobial activity of pradofloxacin indicate that it is most likely that disease dependent changes in the animal's physiological system do not affect its activity.

[1] The terminology of *Staphylococcus intermedius* has changed during the application procedure. *S. intermedius* has been reclassified as a member of the *S. intermedius* group, which also includes *S. pseudintermedius*. A distinct classification of the investigated phenotypically identified *S. intermedius* isolates according to the newly defined species in this group is not possible retrospectively. This should be noted whenever the term *S. intermedius* is used in the following text.

Development of resistance

Resistance to fluoroquinolones has been observed to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alteration to DNA gyrase or topoisomerase IV, (ii) alterations in drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance, and (v) gyrase protection enzymes. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones.

As no officially established breakpoints were available for pradofloxacin, the applicant proposed a breakpoint based on MIC_{90} data and provided susceptibility profiles of the target organisms. The proposed breakpoint for pradofloxacin: susceptible: ≤1 µg/ml, resistant: ≥2 µg/ml is accepted as a preliminary one. At present clinical data are not sufficient to support a higher clinical breakpoint than the proposed microbiological breakpoint. Although this preliminary breakpoint has limitations, particularly as regards clinical relevance, it was used during the procedure as a tool to assess the resistance situation of pradofloxacin as a new substance in the class of fluoroquinolones.

Applying this tentative resistance breakpoint of >2µg/ml, no resistance could be detected in the anaerobic target pathogens. A low incidence of resistance was detected in *S. intermedius* (0.8%) and a higher incidence of resistance was detected in *E. coli* (9.4%). The incidence of resistance for both *E. coli* and *S. intermedius* was slightly higher in cats compared to dogs.

Cross-resistance was confirmed to other fluoroquinolones. A considerably high number of multi-resistant strains were detected, however due to the small data set a clear pattern of co-resistance could not be demonstrated.

Data were provided from four studies on the Mutant Prevention Concentrations (MPC) for *E. coli*, *S. aureus*, *S. intermedius* and *P. gingivalis*. The MPC is used to define the capacity of an antimicrobial to minimise or limit development of resistant organisms. In these studies pradofloxacin exhibited the most favourable characteristics of all the tested fluoroquinolones. However, no standard method is currently available describing the determination of MPCs. Moreover, it is unknown how to integrate MPCs in pharmacodynamic models for specific clinical indications and, hence, how to apply the concept in the design of optimal dosing schemes.

The spectrum of pradofloxacin is broader than for other authorised substances, with a better activity against both Gram-positive bacteria and anaerobes. As pradofloxacin is the first fluoroquinolone authorised as an adjunct in periodontal therapy, it is likely that the overall exposure of dogs to fluoroquinolones will increase. Increased exposure (use) of fluoroquinolones in general, including pradofloxacin, would imply an increased risk of selection and spread of resistance to fluoroquinolones.

As pradofloxacin has not been used during the study period, the data do not allow for conclusions regarding detailed possible effects of a future introduction of pradofloxacin on resistance.

In order to ensure the prudent use of Veraflox Tablets and Veraflox 25 mg/ml Oral Suspension, and to save Veraflox as a second-line antimicrobial, specific risk management advice (as recommended in the current SPC guidance and the CVMP reflection paper on fluoroquinolones) are included in the product literature accordingly.

Target animal tolerance

Dogs

In healthy Beagle dogs aged 8 – 11 months pradofloxacin was well tolerated at the recommended repeated treatment dose and elevated doses over a period of 3 months. No significant adverse effects attributed to treatment were observed, either with the recommended treatment dose or with the 2 X

and 3.3 X the maximum recommended doses. While the target animal safety study did not provide evidence for a treatment related cartilage damage even at overdoses, toxicity studies in Beagle dogs revealed toxic effects in 5 – 6 months old animals already at the therapeutic dose. The clinical studies did not reveal any treatment related adverse effects beyond the ones already known for fluoroquinolones.

Six other target animal safety studies were conducted with Veraflox Tablets in dogs. The study design followed the relevant U.S. guidance documents. The safety of pradofloxacin was assessed at high overdoses in support of the maximum label dose of 12 mg/kg bw for the treatment of urinary tract infections (treatment period 3 days). These studies provide further information of the toxicological profile of pradofloxacin in the dog. The bone marrow and haematopoietic system, as well as the intestinal tract, proved to be the target organs of pradofloxacin toxicity in dogs. Thrombocytopenia and leucopenia were induced at daily oral doses of 27 mg/kg bw, corresponding to 6 X the maximum recommended dose, and above. Severe clinical adverse effects and deaths were induced at daily oral doses of 36 mg/kg bw and above. Intermittent vomiting as well as altered faecal consistency (loose stools) were observed at doses of 12 mg/kg bw (2.7 X the maximum dose). Corresponding information is included in the product literature.

Measures for the safe use of Veraflox Tablets in dogs are adequately addressed in the product literature.

Cats

Veraflox 15 mg Tablets were shown to be well tolerated in cats following daily oral doses of up to 3.3 X the recommended dose, administered for 21 consecutive days. Occasional vomiting, which might have been treatment-related, was the only abnormal clinical finding. The assessment of blood parameters, which were sometimes outside the reference range, remained inconclusive as the reference ranges were not based on historical control data but on data obtained from another experimental study of the company. With respect to the cartilage damaging potential of pradofloxacin, the cats used in this study (11 months old) did not represent the subgroup of growing cats primarily exposed to this effect. This potential has been addressed in a 3 week oral toxicity study in 6 week old kittens. A NOEL of 25 mg/kg was derived for the articular cartilage toxicity of pradofloxacin.

The safety of Veraflox 25 mg/ml Oral Suspension in 8 – 9 month old cats was investigated in a GLP compliant study in which doses of up to 3.3 X the recommended dose were administered once daily for 21 consecutive days. Occasional vomiting, soft faeces and salivation post dosing, which seems to result from high volumes and the formulation of the administered product, were the only abnormal clinical observations.

Two other target animal safety studies were presented, conducted with the tablets and 25 mg/ml oral suspension administered at very high overdoses in cats. The study design followed the relevant U.S. guidance documents. In the target animal safety study using the tablets, the liver and small intestine were shown to be the target organs of toxicity, with histopathological abnormal findings after daily doses of 36 mg pradofloxacin/kg bw (8 X the maximum dose for the tablets) and above. In addition, a small decrease in neutrophils and total protein was found at that dose level. As observed in dogs, infrequent vomiting, salivation and faecal changes were observed at doses of 12 mg/kg bw and above. The highest tested dose of 120 mg/kg bw/ day induced severe toxic effects and all cats in this dose group had to be euthanised for animal welfare reasons before termination of the study.

In another target animal safety study, Veraflox 25 mg/ml Oral Suspension proved to be well tolerated in cats at daily oral doses of 25 and 50 mg/kg bw for 21 and 7 days, respectively (corresponding to 3.3 X and 6.6 X the maximum recommended dose). Occasional vomiting, salivation and soft faeces and mild changes in haematology were observed and considered not to be clinically relevant.

The potential for oculotoxicity of pradofloxacin was investigated in cats, based on ophthalmological examination, fundus investigation using Stratus OTC III, electrophysiological parameters, and post mortem examination including histopathology of the eye including optic nerve. Both a negative and a positive control (enrofloxacin 30 mg/kg bw) were included. Pradofloxacin given at daily doses of 30 and 50 mg/kg bw for 21 and 7 days, respectively, did not induce oculotoxic effects. In contrast, enrofloxacin at daily doses of 30 mg/kg bw clearly induced degenerative changes of the retina.

Measures for the safe use of both the tablets and the 25 mg/ml oral suspension in cats are adequately addressed in the product literature. Information on intermittent vomiting observed at daily oral doses of pradofloxacin corresponding to 2.7 times the maximum recommended dose (tablets) and 1.6 times the maximum recommended dose (suspension) in cats is also included in the product literature.

Laboratory studies:

Dose titration studies

Claims in Dogs:

Pyoderma (superficial and deep)

Three laboratory studies employing a canine superficial pyoderma model were reported for dose finding. The infection model for superficial pyoderma is considered predictive also for deep pyoderma. Two of the studies were suitable to indicate that 3 mg/kg bw was the lowest effective dose and this dose was selected for the pivotal field studies.

Wound infections

A laboratory dose determination study was reported employing an established model of canine surgical wound infection. From this study a minimum effective dose of 3 mg/kg bw was justified.

Urinary tract infections

Two laboratory dose determination studies were reported employing a urinary tract infection model in dogs. However, a therapeutic dose could not be derived properly particularly because of the variable infection rates in the treatment groups, therefore, the selected therapeutic dose of 3 mg/kg bw is solely based on the favourable results of a prospective PK-PD analysis and the high concentrations of pradofloxacin in urine following administration at the recommended dose level.

Periodontal disease

No dose determination study was conducted as experimental models are not available for periodontal disease.

Claims in Cats:

Veraflox 15 mg Tablets:

No dose determination studies were submitted for the indications claimed. Thus, the recommended dose for Veraflox Tablets was only based on PK-PD aspects.

Veraflox 25 mg/ml Oral Suspension:

With one exception (below), no dose determination studies were submitted for the indications claimed. Thus, the recommended dose of the 25 mg/ml oral suspension was based on PK-PD aspects.

Acute infections of the upper respiratory tract

A controlled, blinded, randomised challenge dose determination study, in close compliance with GCP, was conducted which provided sufficient evidence that 5 mg/kg bw pradofloxacin oral suspension is efficacious in the treatment of bacterial secondary infections.

Dose confirmation

Claims in Dogs

Pyoderma (superficial and deep)

A controlled multicentre randomised clinical field trial was conducted in dogs suffering from superficial pyoderma as an exploratory dose-confirmation study, without blinding. The study was considered to have serious shortcomings and was not useful.

Periodontal disease

A controlled exploratory dose-confirmation study under laboratory conditions was conducted in Beagle dogs to investigate periodontal loss of attachment and the natural sub-gingival flora, in cases of periodontal disease using 3 mg pradofloxacin/kg bw administered over 6 days. The positive control was a metronidazole/spiramycin combination product (tablets) administered at 12.5 mg/kg bw metronidazole and 75000 IU/kg bw spiramycin twice a day. The flora which is currently accepted to be pathogenic for the periodontium consists of a variety of Gram-negative anaerobic bacteria. In addition to spirochetes, the organisms found *inter alia* in the study, that is, *Porphyromonas* spp*.* and *Prevotella* spp*.* are primarily involved. The study results demonstrate that pradofloxacin and the positive control were not significantly different in their activity on periodontal loss of attachment and sub-gingival flora. The buccal ecosystem was positively changed in both treatment groups. Pradofloxacin induced a significantly longer beneficial effect on the buccal ecosystem than the control product.

This study, as well as the clinical field study, both employed a "dirty tooth model" which provided a practical method of determining the actual effect of antimicrobial treatment. A relatively short-term effect on gingival flora and a small reduction in pocket depth are the results. The Committee agreed that this is the best which can be expected using such a model without further clinical periodontal therapy, which is according to the approved indications as being the prerequisite of the antimicrobial treatment.

Field trials

Claims in Dogs:

Pyoderma (superficial and deep)

A multicentre, controlled, randomised and blinded clinical field study was carried out on 2 parallel treatment groups of dogs displaying clinical signs of superficial or deep pyoderma to confirm the clinical efficacy of pradofloxacin tablets. Dogs were treated orally with 3 mg/kg pradofloxacin once daily or with a control (combination) product containing 10 mg/kg amoxicillin and 2.5 mg/kg clavulanic acid, given twice daily. The treatment period was 14 - 63 days. The cure rate in superficial pyoderma was 86.36% for pradofloxacin and 81.58% for the control product, with no significant difference between the groups. The prevalence of bacterial strains isolated from superficial and deep pyoderma was too low to prove their causal relationship with the disease except for *Staphylococcus intermedius*. Whilst the efficacy of pradofloxacin for use in superficial pyoderma was considered proven by the trial, the efficacy for deep pyoderma was not supported by these data. A second multi-centre GCP field

study was therefore conducted in dogs suffering from deep pyoderma, and using the same study protocol as the previous study. 86% of the dogs treated with pradofloxacin and 72% of the dogs treated with the control product were cured. The relapse rate was significantly lower for pradofloxacin. The pathogen involved in a sufficient number of clinical cases was *Staphylococcus intermedius*. Based on these data, pradofloxacin was considered efficacious in the treatment of canine deep pyoderma caused by *Staphylococcus intermedius*.

As regards the treatment duration for superficial pyoderma, a sufficient number of animals suffering from superficial pyoderma were cured after a treatment duration of 14 days, with only 25% of the dogs needing a treatment period of longer than 21 days. Thus a treatment duration of 14 – 21 days was considered justified.

As regards the treatment duration for deep pyoderma, a sufficient number of animals suffering from deep pyoderma were cured after a treatment duration of 14 days, although 68% of the dogs needed a longer treatment period of up to 35 days. Thus treatment duration of 14 – 35 days was considered justified.

The treatment duration should be no longer than necessary. Furthermore, the effect of treatment should be assessed regularly during the treatment course. Advice to this effect is therefore included in the SPCs (section 4.9) and Package Leaflets (section 8).

Wound infections

A multicentre, multiregional, controlled, randomised and blinded clinical field study was carried out comparing 2 parallel treatment groups to confirm the clinical efficacy of pradofloxacin tablets in dogs that had wounds from either bites or another trauma. The dogs were treated orally with 3 mg pradofloxacin /kg bw once daily or with a control product, containing 10 mg/kg amoxicillin and 2.5 mg/kg clavulanic acid, twice daily for 7 days. All dogs treated with pradofloxacin were cured at the end of the study. Pradofloxacin proved to be therapeutically non-inferior to the control product. The prevalence of isolated bacterial strains was too low to prove their causal relationship with the disease except for *Staphylococcus intermedius*. Thus, pradofloxacin was considered efficacious for the treatment of wound infections caused by susceptible strains of *Staphylococcus intermedius*, using a treatment duration of 7 days.

Urinary tract infections

A controlled, randomised, multicentre, blinded field trial was conducted in dogs suffering from clinical signs of acute urinary tract infections (UTIs), i.e., cystitis or prostatitis to compare 2 parallel treatment groups in order to confirm the clinical efficacy of pradofloxacin tablets. Dogs were treated orally with 3 mg/kg pradofloxacin once daily or with a control product containing 10 mg/kg amoxicillin combined with 2.5 mg/kg clavulanic acid, twice daily, for 7 - 21 days. It was agreed to consider "bacteriological recovery" (BR) and "clinical recovery" (CR) separately to assess the efficacy of pradofloxacin in canine UTIs. BR and CR are comparable with rates reported from other fluoroquinolones, and the BR was significantly higher than that achieved with the control product. The pathogen involved in a sufficient number of clinical cases was *E. coli*. *Staphylococcus* spp. was identified in 18.6% of cases only. However, taking into account the favourable pre-clinical data on that pathogen, the claim against *Staphylococcus intermedius* is supported. The incidence of *Proteus* spp. in infected dogs was so low that a causal relationship with the disease, and in particular with its cure in the field study, could not be established.

Data for canine UTIs demonstrated that pradofloxacin was efficacious in the treatment of in acute urinary tract infections caused by susceptible strains of *Escherichia coli* and *S. intermedius*. The majority of animals were cured after 7 or 14 days of treatment, and only 14.1% of animals needed a longer treatment period of 21 days. Thus, a treatment period of 7 to 21 days is recommended,

depending on the severity of the disease. Corresponding advice is included in section 4.9 of the SPC (section 8 of the package leaflet).

Periodontal disease

A controlled, randomised, multicentre, blinded field trial, comparing 2 parallel treatment groups of dogs suffering from periodontal disease, was conducted to confirm the efficacy of pradofloxacin tablets (3 mg/kg bw given once daily for 7 days) in the alleviation of clinical signs associated with periodontal disease in dogs. Efficacy was compared to that of a control product (capsules containing clindamycin hydrochloride: 5.5 mg/kg bw given twice daily for 7 days). Both of the antimicrobial treatments (pradofloxacin or clindamycin) induced a significant reduction of pocket depth over the study period at both target teeth. The reduction of pocket depth induced by treatment with either pradofloxacin or clindamycin was similar for all probing sites. No statistically significant difference was detected between the groups for mean bleeding on probing (BOP) score. The BOP score decreased significantly in both groups over the study period. No statistically significant difference was detected between the groups for general condition score. No bacterial strain could be isolated from most of the samples, but from the positive samples *Porphyromonas gingivalis* and *Prevotella intermedia* were the predominant organisms. Pradofloxacin induced a significant reduction of the total subgingival anaerobic count, in contrast to the control product. It was concluded that pradofloxacin was effective in the alleviation of clinical signs associated with periodontal disease in dogs and that it was non-inferior to clindamycin.

The complexity of periodontal diseases in dogs was illustrated by expert reports from recognised specialists in veterinary dentistry. According to these, inconsistent bacteriological findings are commonly observed in dogs due to the mixed character of the periodontal flora, but in general periodontal diseases are associated with a prevalence of Gram-negative anaerobic bacteria. This corresponds with the findings made in the clinical field study. Periodontal treatment consists primarily of mechanical teeth cleaning. However, antibiotic treatment is justified in order to achieve a reduction of pathogens and physiological bacterial flora, and by this detoxification of the periodontium from detrimental bacterial toxins, as this cannot solely be reached by scaling, and for the prevention of local and systemic secondary infections. The latter have been shown to be significantly correlated with periodontal diseases by literature references supplied. By its broad spectrum of antimicrobial activity, pradofloxacin is considered suitable for these purposes.

Based on the data provided, the Committee considered the proposed indication of "As adjunctive treatment to mechanical or surgical periodontal therapy in the treatment of infections of the gingiva and periodontal tissues caused by susceptible strains of anaerobic organisms, for example *Porphyromonas* spp*.* and *Prevotella* spp*.*" as proven, after a treatment period of 7 days with pradofloxacin. However the CVMP was concerned about the use of pradofloxacin without any restriction, for all periodontitis patients; so the Committee took account of current clinical practice, including the recommendation of the American Veterinary Dental College (AVDC) that antimicrobials should only be used as adjunctive therapy for animals that are immune compromised, have underlying disease (such as clinically relevant cardiac, hepatic or renal diseases) and/or when severe oral infection is present. For these reasons the indication was restricted to the adjunctive treatment of severe (only) infections of the gingival and periodontal tissues, and the final indication is therefore "As adjunctive treatment to mechanical or surgical periodontal therapy in the treatment of severe infections of the gingiva and periodontal tissues caused by susceptible strains of anaerobic organisms, for example *Porphyromonas* spp*.* and *Prevotella* spp*.*".

In addition, in order to avoid any misinterpretation and to make it absolutely clear that pradofloxacin should only be used in such patients in which mechanical periodontal procedures are not sufficient, while leaving treatment decisions at the discretion of the veterinarian, the following advice is included in section 4.5 (Special precautions for use in animals) of the Veraflox (Tablet) SPC: "This veterinary

medicinal product should only be used in severe cases of periodontal disease. Mechanical cleaning of teeth and removal of plaque and calculus or extraction of teeth are prerequisites for a persistent therapeutic effect. In case of gingivitis and periodontitis, the veterinary medicinal product should only be used as an adjunct to mechanical or surgical periodontal therapy. Only those dogs for which periodontal treatment goals cannot be achieved by mechanical treatment alone should be treated with this veterinary medicinal product." Similar advice is given in section 11 of the Package Leaflets for Veraflox Tablets.

Claims in Cats:

Veraflox Tablets:

Acute infections of the upper respiratory tract:

A GCP compliant, blinded multicentre field study was carried out comparing two treatment groups to demonstrate the efficacy of pradofloxacin 15 mg tablets in the treatment of feline acute upper respiratory infections. Chronic diseases or infections of the lower respiratory tract including pneumonia were excluded. Cats were treated orally with 3 mg/kg bw pradofloxacin once daily or with a reference product containing potentiated amoxicillin as tablets (12.5 mg/kg bw) twice daily for 5 consecutive days. The treatment results with pradofloxacin were comparable to those obtained with the reference product. The prevalence of isolated bacterial strains was too low to prove their causal relationship with the disease except for *Escherichia coli* and *Staphylococcus intermedius*.

Although MIC data and clinical efficacy were not demonstrated for *Pasteurella multocida* from the tablet studies, the claim is supported. *Pasteurella multocida* is one of the predominant causative pathogens in feline respiratory infection as demonstrated in the studies using the oral suspension formulation. MIC data have shown a high susceptibility to pradofloxacin without indicating resistant isolates, superior results were reached in PK/PD-analysis and good clinical results were presented in the studies with the suspension.

Veraflox 25 mg/ml Oral Suspension:

Acute infections of the upper respiratory tract:

A GCP compliant, multicentre, controlled, randomised and blinded field study was carried out comparing two treatment groups to demonstrate the efficacy of pradofloxacin 25 mg/ml oral suspension in the treatment of feline acute upper respiratory infections. Chronic diseases or infections of the lower respiratory tract including pneumonia were not included. Cats were treated orally with 5 mg/kg bw pradofloxacin once daily or with a reference product (10 mg/kg bw amoxicillin combined with 2.5 mg/kg bw clavulanic acid) twice daily for 5 consecutive days. Non-inferiority of pradofloxacin to the reference product was shown for the primary efficacy criterion, which was complete cure. Pradofloxacin induced a significantly higher bacteriological cure rate than the control product. The prevalence of isolated bacterial strains was too low to prove their causal relationship with the disease except for *Escherichia coli*, *Pasteurella multocida* and *Staphylococcus intermedius*.

Wound infections and abscesses

A GCP compliant, multicentre, controlled, randomised and blinded field study was carried out comparing two treatment groups to demonstrate the efficacy of pradofloxacin 25 mg/ml oral suspension in cats for the treatment of wound infections and abscesses from bites and traumas. Cats were orally treated with 5 mg/kg bw pradofloxacin once daily or with a reference product (10 mg/kg bw amoxicillin combined with 2.5 mg/kg bw clavulanic acid) twice daily for 7 consecutive days. Although a wound score (WS) ≤ 2 is not applicable to demonstrate clinical cure, on day 14 ± 2 only 4

cats in the pradofloxacin group had a WS of 1 still showing swelling or erythema. Non-inferiority between the two treatment groups was shown. The prevalence of isolated bacterial strains was too low to prove their causal relationship with the disease except for *Pasteurella multocida* and *Staphylococcus intermedius*.

Overall conclusions on efficacy

Dogs:

The submitted studies demonstrate the efficacy of Veraflox Tablets administered at doses of 3 mg pradofloxacin/kg bw in the treatment of infected wounds, superficial and deep pyoderma, acute urinary tract infections and as adjunctive treatment to mechanical or surgical periodontal therapy in the treatment of severe infections of the gingiva and periodontal tissues caused by susceptible strains of pathogens. Treatment durations vary considerably depending on each indication. As regards periodontal diseases, additional advice is included in section 4.5 of the SPC (and section 11 of the Package Leaflet) in order to make it very clear that Veraflox should only be used in patients with severe gingivitis or periodontitis, and in patients in which mechanical periodontal procedures alone are not sufficient, while leaving treatment decisions at the discretion of the veterinarian. The Committee considered that this was in line with the recommendations of AVDC.

Target animal safety was demonstrated. Measures for the safe use of the product are necessary and have been addressed in the product literature accordingly.

Cats:

The studies provided demonstrate the efficacy of pradofloxacin tablets administered at doses of 3 mg/kg bw in treatment of acute infections of the upper respiratory tract, and also the efficacy of pradofloxacin 25 mg/ml oral suspension administered at doses of 5 mg/kg bw in treatment of acute infections of the upper respiratory tract, and infected wounds and abscesses. The tolerance of cats aged 6 weeks and older to the recommended treatment dose of Veraflox (pradofloxacin) 15 mg Tablets and Veraflox 25 mg/ml Oral Suspension and for the recommended treatment duration has been demonstrated. Measures for the safe use of the product are necessary and have been addressed in the product literature accordingly.

The following indications for use were justified for Veraflox Tablets:

Dogs:

Treatment of:

- wound infections caused by susceptible strains of the *Staphylococcus intermedius* group (including *S. pseudintermedius*),
- superficial and deep pyoderma caused by susceptible strains of the *Staphylococcus intermedius* group (including *S. pseudintermedius*),
- acute urinary tract infections caused by susceptible strains of *Escherichia coli* and the *Staphylococcus intermedius* group (including *S. pseudintermedius*) and
- as adjunctive treatment to mechanical or surgical periodontal therapy in the treatment of severe infections of the gingiva and periodontal tissues caused by susceptible strains of anaerobic organisms, for example *Porphyromonas* spp*.* and *Prevotella* spp*.*" (see SPC section 4.5)

Cats:

Treatment of acute infections of the upper respiratory tract caused by susceptible strains of *Pasteurella multocida*, *Escherichia coli* and the *Staphylococcus intermedius* group (including *S. pseudintermedius*).

The following indications for use were justified for Veraflox Oral Suspension:

Cats:

Treatment of:

- acute infections of the upper respiratory tract caused by susceptible strains of *Pasteurella multocida*, *Escherichia coli* and the *Staphylococcus intermedius* group (including *S. pseudintermedius*).
- wound infections and abscesses caused by susceptible strains of *Pasteurella multocida* and the *Staphylococcus intermedius* group (including *S. pseudintermedius*).

5. Benefit risk assessment

Introduction

Veraflox 15, 60, and 120 mg Tablets and Veraflox 25 mg/ml Oral Suspension contain pradofloxacin, a novel 3rd generation fluoroquinolone, as the active ingredient.

Veraflox Tablets are intended for the treatment of dogs with the following infections caused by certain specified and susceptible pathogens: wound infections; superficial and deep pyoderma; acute urinary tract infections; and, as adjunctive treatment for severe infections of the gingival and periodontal tissues.

Veraflox Tablets are also intended for the treatment of cats with acute infections of the upper respiratory tract caused by certain specified and susceptible pathogens.

Veraflox 25 mg/ml Oral Suspension is intended only for the treatment of cats with the following infections caused by certain specified and susceptible pathogens: acute infections of the upper respiratory tract; wound infections and abscesses.

Benefit assessment

Direct therapeutic benefit

Veraflox is proposed for the treatment of infected wounds, superficial and deep pyoderma, urinary tract infections and adjunctive treatment in the treatment of severe gingival and periodontal diseases in dogs, and for the treatment of upper respiratory tract infections and infected wounds and abscesses in cats, caused by susceptible pathogens. Systemic antimicrobial treatment of these conditions is accepted veterinary practice. In case of canine periodontal diseases, Veraflox is accepted as adjunctive treatment to mechanical or surgical therapy in the treatment of severe infections of the gingiva and periodontal tissues. This is in line with current clinical practice, including the current recommendations of the AVDC. Appropriate advice is included in the product literature to ensure that antimicrobial treatment as adjunct to mechanical and/or surgical periodontal therapy is limited to patients with severe gingivitis or periodontitis, for which mechanical procedures alone are not considered sufficient by the veterinarian/dentist.

Compared to other fluoroquinolones used in veterinary medicine, pradofloxacin shows a wider spectrum of activity against Gram-positive and anaerobic bacteria. Pradofloxacin shows a concentration dependent bactericidal activity and the resistance rate of the target pathogens is low.

Additional benefits

Veraflox increases the range of available second-line antimicrobials which are used for the treatment of clinical conditions which respond poorly to, or are expected to respond poorly to, other classes of antimicrobials.

Risk assessment

Main potential risks

Quality:

The quality of both Veraflox Tablets and Veraflox Oral Suspension is considered adequate. The applicant has committed to provide some further data pertaining to the validation and stability data from the first three commercial batches for the tablets and the oral suspension, and the specifications will be reviewed on the basis of these results.

Safety:

The acute oral toxicity of the product is very low. In repeat dose toxicity studies the target organs of toxicity were the gastrointestinal tract in rodents and in the dog. At higher doses, degenerative and inflammatory effects in the intestinal tract were seen, as well as changes in the cartilage of knee joints in individual animals. The known risk of quinolone-induced chondropathy in growing dogs is adequately addressed in the SPCs (section 5.3) (and in the package leaflets). In addition to the proposed warning, the use of pradofloxacin in animals with persisting joint lesions has been contraindicated, as lesions may worsen during therapy.

Reproductive toxicity studies in laboratory animals provide evidence of maternotoxic and foetotoxic effects. The safety of pradofloxacin has not been established in queens or bitches during pregnancy and lactation. Therefore, Veraflox Tablets and Oral Suspension must not be used in animals during pregnancy and lactation.

Pradofloxacin was considered non-irritating to the eyes and skin and had no potential to induce skin sensitisation in a guinea pig maximisation test. Pradofloxacin did not induce foetotoxic or teratogenic effects in laboratory animals at doses below maternal toxicity.

The overall pattern of genotoxicity of pradofloxacin is consistent with that of other fluoroquinolone topoisomerase II inhibitors. The genotoxicity of pradofloxacin is threshold related and margin of safety (MOS) assessments can therefore be undertaken.

In the mouse carcinogenicity study, a high dose tumourigenic effect (gall bladder adenoma) was observed at a dose of 7000 ppm following long term administration and is considered to be due to the threshold related mode of action. With regard to the target species, dogs and cats, acceptable MOSs were calculated for the proposed product.

The risks associated with dermal exposure, the most likely route by which a person administering the product is likely to be exposed, were considered to be negligible. For small children (10 kg bodyweight) the accidental intake of Veraflox Tablets or ingestion of Veraflox Oral Suspension could be harmful. In addition to the child resistant closure of the bottle and the blister package of the tablets, appropriate warning phrases are therefore included in the product literature.

Considering that Veraflox is indicated for the individual treatment of companion animals, the environmental risk assessment stops in phase I. The standard advice for disposal of any unused product or waste material is included in the product literature.

The safety of pradofloxacin in the target species, dogs and cats, was demonstrated at up to 2.7 times the recommended dose in dogs and cats, administered once a day and for 3 times the recommended treatment duration. Additional target animal safety studies in dogs and cats which were performed with high overdoses further illustrate the toxicological profile of pradofloxacin. Accordingly, information on observed intermittent vomiting and soft faeces in dogs administered repeated doses corresponding to 2.7 times the maximum recommended dose, and observed intermittent vomiting in cats after repeated doses corresponding to 2.7 times (tablet) and 1.6 times (suspension) the maximum recommended dose, is included in the product literature.

In cats, pradofloxacin at daily oral doses corresponding to 3 and 5 times the maximum recommended dose (suspension) did not induce retinotoxic effects (in contrast to enrofloxacin).

Efficacy

Data on the antimicrobial activity of pradofloxacin, including MIC studies, from various European countries representative of the European region, were provided. Bacterial isolates are from clinical cases including urinary tract infections, pyoderma, wounds and periodontal diseases in dogs, and upper respiratory tract infections, wounds and abscesses in cats. The isolates were tested according to standardised CLSI guidelines and the MIC data confirm the good susceptibility of the claimed target pathogens to pradofloxacin. The figures given in section 5.1 of the SPCs reflect this.

No resistance could be detected in anaerobic target pathogens and only a low incidence of resistance was detected for facultative anaerobic/aerobic pathogens.

Cross-resistance was confirmed to other fluoroquinolones and information is included in the pharmacodynamic sections of the product literature accordingly.

A number of multi-centre GCP field studies were provided. The dose of pradofloxacin was selected based on dose-determination and dose-confirmation studies, and was supported by pharmacodynamic and pharmacokinetic analyses. The efficacy of pradofloxacin at oral doses of 3 mg/kg bodyweight (tablets) and 5 mg/kg bodyweight (suspension) was shown for each claimed indication and proved to be at least equivalent to established reference products. Treatment durations vary considerably depending on the individual indication. Mild gastrointestinal disturbances, including vomiting, were observed in rare cases only. These adverse effects are adequately addressed in the SPCs and package leaflets.

The recommended dose regime of 3-4.5 mg/kg bodyweight for dogs and cats (Veraflox Tablets) and 5-7.5 mg/kg bodyweight for cats (Veraflox Oral Suspension) assists in the optimisation of the margin of safety.

Since this is the first fluoroquinolone indicated for the treatment of periodontal diseases in dogs, it is likely that the overall exposure of dogs to fluoroquinolones will increase. Increased exposure (use) of fluoroquinolones in general, including pradofloxacin, would imply an increased risk of selection and spread of resistance to fluoroquinolones. In addition, a broad spectrum fluoroquinolone will be an attractive choice in many situations other than the authorised indications. This could further increase the overall population exposure.

Risk management or mitigation measures

Appropriate advice is included in the product literature for the tablets in order to emphasise that they should be used for in dogs for dental purposes only in conjunction with mechanical and/or surgical periodontal therapy, and only in dogs with severe gingivitis or periodontitis, for which mechanical procedures alone are not considered sufficient by the veterinarian/dentist (SPC section 4.5).

To minimise the risk of potential overuse of pradofloxacin, specific prudent use warnings are included in the SPC and product literature for both the tablets and oral suspension.

Concerning any environmental risks, the standard advice for disposal of any unused product or waste material is included in the product literature.

Evaluation of the benefit risk balance

Veraflox 15 mg, 60 mg and 120 mg Tablets and Veraflox 25 mg/ml Oral Suspension contain the fluoroquinolone pradofloxacin and are intended for use in cats and dogs, and cats only, respectively, and have been shown to have a positive benefit-risk balance overall.

The therapeutic benefit of these products in the treatment of dogs and cats with infections of the skin, respiratory tract, urinary tract or periodontal/gingival tissues was clearly demonstrated.

Compared to other veterinary fluoroquinolones, pradofloxacin was shown to have a wider antibacterial spectrum of activity against Gram-positive bacteria and anaerobes. Adequate risk mitigation advice has been included in the SPC to take into account the possible risk of non-prudent use of the product and the consequent risk for increase of antimicrobial resistance.

Veraflox is expected to provide an alternative for veterinary practitioners to use in the treatment of clinical conditions which respond poorly to, or are expected to respond poorly to, other classes of antimicrobials. Adequate and sufficient information in relation to the use of Veraflox as a second line antibiotic is included in the product literature.

Pradofloxacin proved to be well tolerated in dogs and cats.

Concerns relating to genotoxicity have been adequately addressed. The overall pattern of genotoxicity of pradofloxacin proved to be consistent with that of other fluoroquinolone topoisomerase II inhibitors. It is threshold related and consequently margin of safety (MOS) assessments can be undertaken. With regard to the target species, dogs and cats, acceptable MOSs could be calculated from a valid mouse carcinogenicity study. These MOSs indicate that the carcinogenic risk associated with the therapeutic use of this product is negligible.

Also for the user, in particular children at risk of accidental ingestion of tablets or suspension, adequate MOSs were calculated.

With regard to potential risks to both the target species and the user, appropriate and adequate information and warning statements are included in the product literature to ensure the safe and correct use of these products.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of Veraflox were considered to be in accordance with the requirements of Council Directive 2001/82/EC as amended, and that the benefit-risk balance was favourable.