Zeniquin® (marbofloxacin) Tablets

For the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin

NADA 141 - 151

Pfizer Inc.

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FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

NADA Number: 141-151

Sponsor: Pfizer Inc
235 East 42nd St.
New York, NY 10017

Generic Name: Marbofloxacin

Trade Name: Zeniquin®

Marketing Status: Rx: U.S. Federal law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits the extralabel use of this drug in food-producing animals.

Effect of Supplement: Provides for the use of Zeniquin (marbofloxacin) tablets in cats as indicated below.

II. INDICATIONS FOR USE

Zeniquin (marbofloxacin) tablets are indicated for the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

Zeniquin tablets should be administered orally to dogs and cats at a dosage of 1.25 mg/lb of body weight once daily, but the dosage may be increased to 2.5 mg/lb.

For the treatment of skin and soft tissue infections, Zeniquin tablets should be given for two to three days beyond the cessation of clinical signs for a maximum of 30 days. For the treatment of urinary tract infections, Zeniquin tablets should be administered for at least 10 days. If no improvement is noted within 5 days, the diagnosis should be re-evaluated and a different course of therapy considered.

Zeniquin is available in strengths of 25, 50, 100, and 200-mg scored, film-coated tablets. Only the 25-mg tablet is labeled for use in cats.

IV. EFFECTIVENESS

A. Dosage Characterization

The effective dosage of marbofloxacin tablets in cats, 1.25 mg/lb body weight orally once daily, was selected based upon an evaluation of the *in vitro* activity of the molecule combined with an assessment of pharmacokinetic data. The similarity between canine and feline plasma concentrations and pharmacokinetic indices provides the rationale for the dose. This dosage has been confirmed as effective in a multi-center clinical effectiveness study, which also demonstrated the *in vitro* antimicrobial susceptibility of bacterial pathogens isolated from cats.

Following are summaries of the *in vitro* activity of marbofloxacin against field isolates of bacterial pathogens collected in the multi-center clinical effectiveness study and a summary of the pivotal pharmacokinetic study.

During the pivotal clinical field study, minimum inhibitory concentrations (MIC) of pathogens were determined using National Committee for Clinical Laboratory Standards (NCCLS) methodology. Table 1 provides a summary of frequent pathogens from the study (Study Number MB-G-5002-94).

Table 1: Summary of marbofloxacin MIC values against pathogens isolated from skin and soft tissue infections in cats enrolled in clinical studies conducted in 1995 and 1998.

		Minimum Inhibitory Concentration (μg/mL)		
Microorganism	n	MIC_{50}	MIC_{90}	Range
Pasteurella multocida	135	0.03	0.06	≤0.008 - 0.25
Beta-hemolytic *Streptococcus*	22	1	1	0.06 - 1
Staphylococcus aureus	21	0.25	0.5	0.125 - 1
Corynebacterium species	14	0.5	1	0.25 - 2
Staphylococcus intermedius	11	0.25	0.5	0.03 - 0.5
Enterococcus faecalis	10	2.0	2.0	1.0 - 2.0
Escherichia coli	10	0.03	0.03	0.015 - 0.03
Bacillus species	10	0.25	0.25	0.125 - 0.25

Plasma pharmacokinetics in cats: Study Number MB/G/F/GB/94/4121

Purpose: To evaluate the plasma concentrations of marbofloxacin in cats after oral dosing of tablets at 2.5 mg/lb (5.5 mg/kg)

Investigator: S.E. Blanchflower
Pfizer Animal Health
Walton Oaks, Tadworth, Surrey, UK

Animals: 7 male cats, 7.7-10.6 lb (3.5-4.8 kg)

Dosage Group: Marbofloxacin 2.5 mg/lb (5.5 mg/kg)

Dosage Form: Proposed commercial formulation tablets

Route of Administration: Oral

Frequency of Treatment: Single administration

Duration of Study: 72 hours

Parameters Measured: Plasma concentrations of marbofloxacin were determined in blood samples collected at 0.33, 0.66, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dosing. Marbofloxacin concentrations in plasma were determined by a validated high performance liquid chromatography (HPLC) assay procedure.

Results: Mean pharmacokinetic parameters are in Table 2 below.

Table 2: Mean pharmacokinetic parameters following a single oral dose of 2.5 mg/lb marbofloxacin in cats.

Parameter	Mean ± SD* n=7		
$AUC_{0 \text{ to inf}}$ (µg•h/mL)	70	±	6
C_{max} (µg/mL)	4.8	±	0.7
T_{max} (h)	1.2	±	0.6
$t_{1/2\,\beta}$ (h)	12.7	±	1.1

* Standard deviation

Conclusions: Based on the terminal elimination half-life and the dosing interval, steady-state levels are reached after the third dose and are expected to be approximately 35% greater than those achieved after a single dose.

Adverse Drug Reactions: None observed.

B. Dose Confirmation

Clinical Field Study - Feline skin and soft tissue
Study Number MB-G-5002-94

Purpose: To determine the effectiveness and field safety of marbofloxacin oral tablets in the treatment of naturally-occurring skin and soft tissue bacterial infections in cats.

Investigators:

Dr. Nancy Brown Plymouth Meeting, PA	Dr. Donna Rauch Grayslake, IL
Dr. David Hancock Victor, NY	Dr. Robert McLain Addison, IL
Dr. Richard Benjamin Berkeley, CA	Dr. Marc Leven Grand Rapids, MI
Dr. Marilyn Pachorek Los Gatos, CA	Dr. Larry Rothe Concord, CA
Dr. Frances Woodworth Batavia, NY	Dr. Georgia Molek Livermore, CA
Dr. Lynn Buzhardt Zachary, LA	Dr. Brett Berryhill Baton Rouge, LA
Dr. Phillip Callahan Orlando, FL	Dr. Roger Sifferman Springfield, MO
Dr. Karen Sama/ Dr. Don Shlange Antioch, CA	Dr. David Lukof Harleysville, PA
Dr. JoAnna Bender Rochester, NY	Dr. Andrew Pickering Terre Haute, IN

Dr. Stuart Gluckman
Mendon, NY

Dr. Kirsten Marshall
Belmont, MI

Dr. Peter Davis
Augusta, ME

Animals:

Cats presenting with bacterial infections of skin and soft tissue were assigned randomly to one of three treatment groups according to a masked study design.

The cats ranged from 8 months to 15 years of age and weighed between 5 and 22.6 lb on the first day of treatment. Of the 259 cases enrolled in the study, 178 could be evaluated for effectiveness. There were one hundred and eighteen males and 60 females. Most of the cases that could not be evaluated had negative pre-treatment culture results.

Dosage Groups: Marbofloxacin 1.25 mg/lb
Marbofloxacin 2.5 mg/lb
Amoxicillin trihydrate 50 mg

Eighty of the evaluable cases were in the marbofloxacin 1.25 mg/lb group, 17 were in the marbofloxacin 2.5 mg/lb group, and 81 were in the active control group.

The higher-dose marbofloxacin group had fewer cases because this group was discontinued during the study. This group was discontinued because, during a concurrent safety study in 8 month old cats, a single cat dosed with 2.5 mg/lb for 42 days showed microscopic articular cartilage changes. A subsequent safety study showed that marbofloxacin does not cause articular cartilage changes at doses up to 7.5 mg/lb in adult cats. When the clinical field study resumed, all cats enrolled were dosed at 1.25 mg/lb because treatment of cats at the upper end of the dosage range was not necessary to evaluate the effectiveness, and fewer treatment groups expedited completion of the study.

Dosage Forms: Marbofloxacin - proposed commercial formulation tablets
Amoxicillin trihydrate- commercial tablets

Route of Administration: Oral

Frequency of Treatment: Once daily

Duration of Study: Maximum of 14 days

Pertinent Parameters Measured: Physical examination and lesion evaluation, bacteriological culture and susceptibility (minimum inhibitory concentration (MIC) determination), hematology, and blood chemistry panels were conducted.

Results: The primary parameter for determination of effectiveness was complete clinical resolution of the infection (no signs of active infection) 5 to 7 days after conclusion of therapy. Clinical resolution is summarized by treatment group in Table 3. One-sided 95% confidence bounds were constructed for the primary variable around the observed difference between the Marbofloxacin treatment groups and the Amoxicillin group. These results are presented in Table 4. Note that there were many fewer subjects in the 2.5 mg/lb Marbofloxacin treatment group than in the other two groups.

Evaluation of hematology and serum chemistry data revealed no clinically significant changes.

Table 3: Summary of complete clinical resolution by treatment.

Marbofloxacin						Amoxicillin		
1.25 mg/lb			2.5 mg/lb			50 mg		
Number of Cases			Number of Cases			Number of Cases		
Resolved	Total	%	Resolved	Total	%	Resolved	Total	%
70	80	87.5	14	17	82.4	71	81	87.7

Table 4: Observed differences in complete clinical resolution between Marbofloxacin and Amoxicillin and 1-sided 95% confidence bound

Marbofloxacin – Amoxicillin			
1.25 mg/lb		2.5 mg/lb	
Observed difference (%)	95% Lower confidence bound (%)	Observed difference (%)	95% Lower confidence bound (%)
-0.2	-8.7	-5.3	-21.6

Conclusions: Marbofloxacin administered orally to cats at 1.25 mg/lb once daily for up to 14 days was safe and effective in the treatment of bacterial infections of skin and soft tissue.

Adverse Drug Reactions: While some cases were not evaluable for effectiveness, all cases were reviewed for purposes of evaluating field safety (adverse events). Of the 259 cases initially enrolled in the study, 115 were in the marbofloxacin 1.25 mg/lb group, 31 were in the marbofloxacin 2.5 mg/lb group, and 113 were in the amoxicillin group. Of the cases treated with 1.25 mg/lb of marbofloxacin, 6 cases had clinical signs possibly related to drug therapy. The following clinical signs were reported (number of cases in parenthesis): diarrhea (3), soft stool (2), vomiting (1). Of the cases treated with amoxicillin, 8 cases had clinical signs possibly related to drug therapy. The following clinical signs were reported: diarrhea (4), vomiting (3), decreased appetite, lethargy/decreased activity (1). There were no adverse clinical signs considered possibly related to drug therapy in the marbofloxacin 2.5 mg/lb treatment group.

V. ANIMAL SAFETY

A. Drug Tolerance Study: Study MB-G-1002-94

Purpose: To assess the toxicological effects of marbofloxacin when administered at a dose of 25 mg/lb (10X the upper limit of the effective dose) once daily for 14 days.

Investigator: L. Bernier
Bio-Research Laboratories Ltd.
87 Senneville Rd.
Senneville, Quebec, Canada

Animals: Twelve cats, approximately eight months of age, weighing 2.7 to 4.5 kg were randomly allocated to two groups containing three males and three females each.

Dosage Groups: Placebo
Marbofloxacin, 25 mg/lb
(10X the upper limit of the effective dose)

Route of Administration: Oral

Frequency of Treatment: Once daily

Duration of Study: 14 days

Parameters Measured: Clinical observations, physical examinations, food consumption, body weight, ophthalmic examinations, lameness evaluations, clinical pathology, gross pathology, and histopathology.

Results:

Male and female cats in the marbofloxacin-treated group exhibited clinical signs consistent with drug intolerance. These signs included, in decreasing order of frequency, excessive salivation, reddened pinnae, increased vocalization, emesis, and hypoactivity. Daily food consumption was lower among treated animals than controls. Weekly body weights revealed marginal weight losses in three of three treated males and one of three treated females. Ophthalmoscopy revealed no treatment-related eye abnormalities. Hematology and serum chemistry revealed no meaningful alterations, and all post-treatment values remained within the normal range. Urinalyses did not reveal any treatment-related changes. Weekly lameness examinations did not reveal any evidence of lameness.

Necropsy organ weight data did not reveal any treatment-related changes. Histopathologically, perivascular and/or diffuse dermatitis was seen in the pinnae of six of six treated cats and less frequently in the standard inguinal skin samples from animals from that group. Mild to moderate lymphoid atrophy of the thymus gland, which is known to occur following stress, was present in five of six treated cats. Chondropathy, characterized by a detachment of the superficial articular cartilage, clumping of collagen fibrils, and anomalies of chondrocyte morphology in the vicinity of the defect, is typical of fluoroquinolone toxicity, and was present in two of six treated cats. One treated male had a duodenal mucosal erosion and one treated female had a pyloric ulcer.

Conclusions:
Clinical signs associated with drug intolerance were ptyalism, erythematous dermatitis, decreased food consumption, and emesis. Pathologic findings included perivascular to diffuse eosinophilic dermatitis, lymphoid atrophy of the thymus gland, articular chondropathy and abnormalities of the gastrointestinal mucosa.

B. Margin of Safety Study: Study MB-G-1003-94

Purpose: To evaluate the safety of marbofloxacin in cats when administered at 2.5, 7.5 or 12.5 mg/lb (1X, 3X, or 5X the upper limit of the clinically effective dose) once daily for 42 days.

Investigator: L. Bernier
Bio-Research Laboratories Ltd.
87 Senneville Rd.
Senneville, Quebec, Canada

Animals: Thirty-two cats approximately eight months of age, weighing 2.6 to 4.3 kg, were randomly allocated to four treatment groups containing four males and four females each.

Dosage Groups: Placebo

Marbofloxacin 2.5 mg/lb
(1X the upper limit of the clinically effective dose)

Marbofloxacin 7.5 mg/lb
(3X the upper limit of the clinically effective dose)

Marbofloxacin 12.5 mg/lb
(5X the upper limit of the clinically effective dose)

Route of Administration: Oral

Frequency of Treatment: Once daily

Duration of Study: 42 days

Parameters Measured: Clinical observations, physical examinations, food consumption, body weight, ophthalmic examination, lameness evaluations, clinical pathology, gross pathology, and histopathology.

Results: Treatment-related clinical findings observed during the course of the study consisted of varying degrees of salivation, and redness and scabbing of ear pinnae in some high-dose (12.5 mg/lb) animals.

Slight to severe salivation was observed continuously or intermittently after Day 5 during the dosing procedure in four of eight high-dose (12.5 mg/lb) cats. Redness of ear pinnae was seen in two high-dose (12.5 mg/lb) females beginning on Days 9 and 14, respectively. Neither finding was recorded in controls or in other marbofloxacin-treated groups. Foamy vomitus and soft stools were noted one time each in one male and one female (respectively) in the high-dose (12.5 mg/lb) group. Due to their low and sporadic incidence, these findings were considered incidental to treatment.

Lameness evaluations did not reveal any clinical evidence of lameness in any cat. There were no changes in mean body weight or body weight gain data that could be attributed to treatment with marbofloxacin. Ophthalmologic examinations revealed no treatment-related findings. A repeated measures ANCOVA, that included treatment, time, their interaction, and the average baseline value in the model, found that decreased segmented neutrophil counts, which were sometimes associated with decreased total leukocyte counts, were observed in all treatment groups; however, the mean counts were statistically significantly lower in the marbofloxacin treated groups relative to the placebo ($p<0.10$ for all treated groups). In some cats, absolute neutrophil counts were below normal reference values. Other hematology, serum chemistry, and urinalysis examinations did not reveal any treatment-related changes. Organ weight data did not reveal any treatment-related changes.

Macroscopic and microscopic examinations revealed treatment-related pathologic changes in skin and articular cartilage of marbofloxacin-treated animals. A perivascular to diffuse dermatitis was reported in one mid-dose (7.5 mg/lb) and four high-dose (12.5 mg/lb) females. Macroscopic articular cartilage erosions of the distal femur were detected in three of eight high-dose (12.5 mg/lb) and one of eight mid-dose (7.5 mg/lb) animals. Microscopic examination revealed a focal or multifocal chondropathy in the animals with macroscopic lesions as well as one low-dose (2.5 mg/lb) animal and an additional high-dose (12.5 mg/lb) animal. The chondropathy was characterized by detachment or fissure of the superficial articular cartilage, abnormal clumping of the collagen fibrils and/or anomalies of chondrocytes such as localized hypercellularity, formation of cell clusters or, less frequently, pyknotic or swollen chondrocytes in the vicinity of the cartilaginous defect.

Conclusions: Gross and histopathological changes in the articular cartilage were produced when cats approximately eight months of age were administered marbofloxacin orally at 7.5 and 12.5 mg/lb for 42 days. Histopathological changes to articular cartilage were also seen in one cat receiving 2.5 mg/lb daily (1X the upper end of the dose range). There was no evidence of lameness during the study. Eosinophilic dermatitis in female animals was associated with administration of marbofloxacin at 7.5 and 12.5 mg/lb for 42 days.

C. Safety Margin (Articular Cartilage) Study:

Purpose: To evaluate the effect of marbofloxacin on articular cartilage of adult cats when administered orally at 1.25, 3.75 and 7.5 mg/lb once daily for 42 days.

Investigator: Elizabeth Evans
Midwest Research Institute
Kansas City, MO

Animals: Forty cats, approximately 12 to 14 months of age, weighing 2.6 to 5.0 kg, were randomly allocated to four groups containing five males and five females each.

Dosage Groups: Placebo

Marbofloxacin 1.25 mg/lb
(1X the lower limit of the clinically effective dose)

Marbofloxacin 3.75 mg/lb
(3X the lower limit of the clinically effective dose)

Marbofloxacin 7.5 mg/lb
(6X the lower limit of the clinically effective dose)

Route of Administration: Oral

Frequency of Treatment: Once daily

Duration of Study: 42 days

Parameters Measured: Clinical observations, physical examinations, body weight, lameness examinations, gross pathology and histopathology of four major diarthrodial joints.

Results: Clinical findings observed during the course of the study consisted of varying degrees of vomiting (emesis) and soft stools, which occurred in all treatment groups including placebo, and increased in frequency with increasing dosage and duration of treatment. There were no treatment-related pathological changes in the joints or other tissues in any marbofloxacin-treated cats.

Lameness examinations conducted once prior to start of treatment and weekly during the treatment period recorded altered movement in two of forty animals. One cat in the control (placebo) group exhibited lameness following trauma to the left rear foot on Day 25. One cat in the high-dose (7.5 mg/lb) group exhibited bilateral hind limb gait alteration from Day 35 through Day 42. The cat did not evince pain upon manipulation or deep palpation, and was never reluctant to move, jump, or to bear weight on the affected limbs. The cause of the abnormal gait was not determined, but the lack of pain or reluctance to bear weight, in addition to the lack of corroborating lesion macroscopically or microscopically, do not support a quinolone-induced lameness. The signs are more consistent with iatrogenic trauma due to restraint during dosing.

Conclusions: No gross or histopathological changes in articular cartilage or other tissues were produced by treatment of skeletally mature cats with marbofloxacin administered orally at 1.25, 3.75 and 7.5 mg/lb/day for 42 days.

VI. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental NADA. This drug is to be labeled for use in dogs and cats only, which are non-food animals.

Human Warnings are provided on the product label as follows: “For use in animals only. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation

persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to fluoroquinolones should avoid contact with this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight."

VII. AGENCY CONCLUSIONS

The data in support of this supplemental NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that Zeniquin® (marbofloxacin) Tablets for cats are safe and effective when used under labeled conditions.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the diagnosis of skin and soft tissue infections, management of the conditions, and monitoring of possible adverse effects of the drug.

Under the Center's supplemental approval policy 21 CFR 514.106(b)(2), this is a Category II change. However, this action did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new species for which the supplemental application was approved.

Pfizer, Inc. holds two patents on this product as follows:

US4801584 expires September 8, 2007
US4864023 expires September 8, 2007

VIII. Labeling (Attached)

A. Package Insert
B. Inner Package Label
C. Outer Package Label

Copies of these labels may be obtained by writing to the:
Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855