

NADA# 141-151

Zeniquin<sup>™</sup>  
(marbofloxacin tablets for dogs)

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

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Zeniquin<sup>®</sup>

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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.

### II. INDICATIONS FOR USE

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

Clinical effectiveness was confirmed in skin and soft tissue infections and urinary tract infections (cystitis) associated with bacteria susceptible to marbofloxacin.

### III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

**Dosage and Administration:** Zeniquin™ tablets should be administered orally to dogs at a dosage of 1.25 mg/lb of body weight once daily, but the dosage may be safely increased to 2.5 mg/lb. Some factors to be considered in the determination of dosage are the nature and severity of the infection, the susceptibility of the pathogen, and ability of the patient to combat infection.

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 four strengths of 25 mg, 50 mg, 100 mg, and 200 mg scored, film-coated tablets.

#### IV. EFFECTIVENESS

##### A. Dose Rationale

The effective dosage of marbofloxacin tablets in dogs, 1.25 mg/lb body weight administered orally once daily, was selected based upon an evaluation of the *in vitro* activity of the molecule combined with an assessment of pharmacokinetic data summarized below. This dosage has been confirmed as efficacious in clinical effectiveness studies, and was not shown to be less effective than a higher dosage of 2.5 mg/lb. Marbofloxacin possesses an *in vitro* potency and spectrum that, when combined with the knowledge of this class of antimicrobial agents, predicts the drug's effectiveness against many canine pathogens. Studies of marbofloxacin pharmacokinetics and tissue concentrations suggest that the drug, when administered orally at 1.25 mg/lb body weight once daily, is delivered to the sites of infection in concentrations which are adequate in magnitude and/or duration to be effective against the majority of canine bacterial pathogens associated with skin, soft tissue and urinary tract infections.

##### 1. *In vitro* Activity

Table 1 provides a summary of the *in vitro* activity of marbofloxacin against field isolates of bacterial pathogens collected in the two clinical effectiveness studies (Study Numbers MB-G-5000-94 and MB-G-5001-94). Minimum inhibitory concentrations (MICs) of pathogens were determined using National Committee for Clinical Laboratory Standards (NCCLS).

Table 1: MIC values\* ( $\mu\text{g/mL}$ ) of marbofloxacin against pathogens isolated from skin, soft tissue and urinary tract infections in dogs enrolled in clinical effectiveness studies conducted during 1994-1996.

Organism	Number of Isolates	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range
<i>Staphylococcus intermedius</i>	135	0.25	0.25	0.125 - 2
<i>Escherichia coli</i>	61	0.03	0.06	0.015 - 2
<i>Proteus mirabilis</i>	35	0.06	0.125	0.03 - 0.25
Beta-hemolytic <i>Streptococcus</i> , (not Group A or Group B)	25	1	2	0.5 - 16
<i>Streptococcus</i> , Group D enterococcus	16	1	4	0.008 - 4
<i>Pasteurella multocida</i>	13	0.015	0.06	$\leq 0.008$ - 0.5
<i>Staphylococcus aureus</i>	12	0.25	0.25	0.25 - 0.5
<i>Enterococcus faecalis</i>	11	2	2	1 - 4
<i>Klebsiella pneumoniae</i>	11	0.06	0.06	0.01 - 0.06
<i>Pseudomonas</i> species	9	**	**	0.06 - 1
<i>Pseudomonas aeruginosa</i>	7	**	**	0.25 - 1

\* The correlation between *in vitro* susceptibility data (MIC) and clinical response has not been determined.

\*\*MIC<sub>50</sub> and MIC<sub>90</sub> not calculated due to insufficient number of isolates.

## 2. Plasma Pharmacokinetics and Tissue Distribution

### a. Plasma pharmacokinetic study in dogs: Study Number 1961N-60-96-205

Purpose: To evaluate the plasma pharmacokinetics in dogs of orally administered marbofloxacin tablets at dosages of 1.25 mg/lb and 2.5 mg/lb.

Investigator: Terri L. Morton  
Midwest Research Institute  
Kansas City, MO

Animals: 12 beagle dogs (6 male, 6 female), 6 animals per group

Dosage Groups: T1: Marbofloxacin 1.25 mg/lb  
T2: Marbofloxacin 2.5 mg/lb

Dosage Form: Proposed commercial formulation tablets

Route of Administration: Oral

Frequency of Treatment: Single administration

Duration of Study: 48 hours

Parameters Measured: Plasma concentrations of marbofloxacin were determined in blood samples collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 36, and 48 hours post-dosing. Marbofloxacin concentrations in plasma were determined by a validated high performance liquid chromatography (HPLC) assay procedure.

Results: Mean pharmacokinetic parameters are summarized in Table 2 below.

Table 2: Mean pharmacokinetic parameters following oral administration of marbofloxacin tablets to adult beagle dogs at a dosage of 1.25 mg/lb or 2.5 mg/lb.

Parameter	Estimate ± SD* (1.25 mg/lb) n=6	Estimate ± SD* (2.5 mg/lb) n=6
Time of maximum concentration, T <sub>max</sub> (h)	1.5 ± 0.30	1.8 ± 0.3
Maximum concentration, C <sub>max</sub> , (µg/mL)	2.0 ± 0.2	4.2 ± 0.5
AUC <sub>0-inf</sub> (µg•h/mL)	31.2 ± 1.6	64 ± 8
Terminal plasma elimination half-life, t <sub>1/2</sub> (h)	10.7 ± 1.6	10.9 ± 0.6

\* SD = standard deviation

Adverse Drug Reactions: None observed

b. Intravenous Pharmacokinetics in the Dog: Study Number MB/-/D/GB/94/4127

Purpose: To evaluate plasma concentrations following a single intravenous (i.v.) administration of marbofloxacin 10% solution at a dosage of 2.5 mg/lb in dogs

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

Animals: 6 beagle dogs (3 male, 3 female)

Dosage Groups: All 6 dogs treated with marbofloxacin at 2.5 mg/lb

Dosage Form: 10% solution

Route of Administration: Intravenous

Frequency of treatment: Single administration

Duration of Study: 72 hours

Pertinent Parameters Measured: Plasma concentrations of marbofloxacin were determined in blood samples collected at 0, 0.1, 0.25, 0.33, 0.67, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hours post-dosing. Marbofloxacin concentrations in plasma were determined by a validated HPLC assay procedure.

Results: Mean pharmacokinetic parameters are summarized in Table 3 below.

Table 3: Mean pharmacokinetic parameters following intravenous administration of marbofloxacin to six adult beagle dogs at a dosage of 2.5 mg/lb.

Parameter	Estimate ± SD* n=6
Total body clearance, (mL/h•kg)	94 ± 8
Volume of distribution at steady state, V <sub>ss</sub> , (L/kg)	1.19 ± 0.08
AUC <sub>0-inf</sub> , (µg•h/mL)	59 ± 5
Terminal plasma elimination half-life, t <sub>1/2</sub> , (h)	9.5 ± 0.7

\* SD = standard deviation

Adverse Drug Reactions: None observed

c. Plasma and tissue concentrations in dogs: Study Number 1961N-60-96-204

Purpose: To evaluate tissue concentrations following oral administration of marbofloxacin tablets at dosages of 1.25 mg/lb and 2.5 mg/lb in dogs.

Investigator: Terri L. Morton  
Midwest Research Institute  
Kansas City, MO

Animals: 24 male beagle dogs, 4 animals per treatment group per sample time

Dosage Groups: T1, T3, T5: Marbofloxacin 1.25 mg/lb  
T2, T4, T6: Marbofloxacin 2.50 mg/lb

Dosage Form: Proposed commercial formulation tablets

Route of Administration: Oral

Frequency of Treatment: Single administration

Duration of Study: 24 hours

Pertinent Parameters Measured: Tissue and fecal concentrations of marbofloxacin were determined at 2, 18, and 24 hours post-dosing. Concentrations were determined by a validated HPLC assay procedure.

Results: Marbofloxacin concentrations of samples are summarized in Tables 4a and 4b.

Table 4a: Tissue distribution of marbofloxacin following a single oral administration of marbofloxacin tablets to adult beagle dogs at a dosage of 1.25 mg/lb.

Tissue	Marbofloxacin Concentrations ( $\mu\text{g/g} \pm \text{SD}$ )		
	2 hours (n=4)	18 hours (n=4)	24 hours (n=4)
bladder	4.8 $\pm$ 1.1	2.6 $\pm$ 1.5	1.11 $\pm$ 0.19
bone marrow	3.1 $\pm$ 0.5	1.5 $\pm$ 1.5	0.7 $\pm$ 0.2
feces	15 $\pm$ 9	48 $\pm$ 40	26 $\pm$ 11
jejunum	3.6 $\pm$ 0.5	1.3 $\pm$ 1.0	0.7 $\pm$ 0.3
kidney	7.1 $\pm$ 1.7	1.4 $\pm$ 0.5	0.9 $\pm$ 0.3
lung	3.0 $\pm$ 0.5	0.8 $\pm$ 0.2	0.57 $\pm$ 0.19
lymph node	5.5 $\pm$ 1.1	1.3 $\pm$ 0.3	1.0 $\pm$ 0.3
muscle	4.1 $\pm$ 0.3	1.0 $\pm$ 0.3	0.7 $\pm$ 0.2
prostate	5.6 $\pm$ 1.4	1.8 $\pm$ 0.6	1.1 $\pm$ 0.4
skin	1.9 $\pm$ 0.6	0.41 $\pm$ 0.13	0.32 $\pm$ 0.08

Table 4b: Tissue distribution following a single oral administration of marbofloxacin tablets to adult beagle dogs at a dosage of 2.5 mg/lb.

Tissue	Marbofloxacin Concentrations ( $\mu\text{g/g} \pm \text{SD}$ )					
	2 hours (n=4)		18 hours (n=4)		24 hours (n=4)	
bladder	12	$\pm$ 4	6	$\pm$ 7	1.8	$\pm$ 0.4
bone marrow	4.6	$\pm$ 1.5	1.28	$\pm$ 0.13	0.9	$\pm$ 0.3
feces	18	$\pm$ 3	52	$\pm$ 17	47	$\pm$ 28
jejunum	7.8	$\pm$ 1.1	2.0	$\pm$ 0.3	1.1	$\pm$ 0.3
kidney	12.7	$\pm$ 1.7	2.7	$\pm$ 0.3	1.6	$\pm$ 0.2
lung	5.48	$\pm$ 0.17	1.45	$\pm$ 0.19	1.0	$\pm$ 0.2
lymph node	8.3	$\pm$ 0.7	2.3	$\pm$ 0.5	2.03	$\pm$ 0.06
muscle	7.5	$\pm$ 0.5	1.8	$\pm$ 0.3	1.20	$\pm$ 0.12
prostate	11	$\pm$ 3	2.7	$\pm$ 1.0	2.0	$\pm$ 0.5
skin	3.20	$\pm$ 0.33	0.705	$\pm$ 0.013	0.46	$\pm$ 0.09

Adverse Drug Reactions: None observed

### 3. Conclusions

Marbofloxacin tablets are rapidly and almost completely absorbed from the gastrointestinal tract following oral administration to fasted animals. The absolute bioavailability following dosing of oral tablets to the same animals was 94%. Absorption of orally administered marbofloxacin increases proportionally over the dose range of 1.25 to 2.5 mg/lb. Marbofloxacin is widely distributed in body tissues. Based on the plasma terminal elimination half-life and the dosing interval, steady-state levels are reached after the third dose and are expected to be approximately 25% greater than those achieved after a single dose.

#### B. Dose Confirmation

##### 1. Clinical Field Study - Canine Urinary Tract Infections (Cystitis) Study Number MB-G-5001-94

Purpose: To demonstrate the effectiveness and safety under field conditions of a dose of 1.25 mg/lb of marbofloxacin for the treatment of urinary tract infections (cystitis) in dogs.

Investigators:

Dr. M. Bernstein  
Boston, MA

Dr. L. Buzhardt  
Zachary, LA

Dr. J. Bender  
Rochester, NY

Dr. K. Sama/Dr. D. Schlange  
Antioch, CA

Dr. D. Rauch  
Mundelein, IL

Dr. D. Hancock  
Victor, NY

Dr. M. Tichacek/Dr. L. Gustavsen  
Lake Zurich, IL

Dr. M. Daehler  
Waukegan, IL

Dr. M. Leven  
Grand Rapids, MI

Dr. G. Molek  
Livermore, CA

Dr. P. Davis  
Augusta, ME

Animals: In order to participate in the studies, dogs had to have clinical evidence of bacterial cystitis. In order to continue in the study, confirmation of infection by bacterial culture and identification of the pathogen(s) was required. Of the 151 client-owned dogs initially enrolled in the study, 87 were evaluated for effectiveness. Of the 64 unevaluable cases, the majority (51) were lost to effectiveness analysis because of negative pre-treatment bacterial culture results. Of the 87 evaluable cases, 40 of the cases were in the marbofloxacin group and 47 cases were in the active control group. Thirty-four various breeds were represented in the study, in addition to mixed breed dogs. Dogs ranged from 1 year to 15 years of age. Body weights ranged from 6.6 lb to 132.6 lb. Seventy-seven dogs were female and ten were male.

Dosage Groups: Marbofloxacin 1.25 mg/lb  
Sulfadiazine/Trimethoprim (SDZ/TMP) 12.0 mg/lb

Dosage Forms: Marbofloxacin - proposed commercial formulation tablets  
SDZ/TMP - approved commercial tablets

Route of Administration: oral

Frequency of Treatment: Once daily for 10 to 14 days

Duration of Study: Maximum of 14 days

Pertinent Parameters Measured: Parameters included evaluation of clinical signs of urinary tract infection (cystitis), urine bacteriological culture and susceptibility testing, hematology and blood chemistry. The primary parameter of effectiveness was the elimination of all pathogens originally cultured at pre-treatment examination. The study was conducted according to a blinded, controlled, randomized design.

Results: Microbiological cure rates (case by case) of 97.2% and 95.3% were observed in the marbofloxacin and SDZ/TMP groups, respectively. Based upon clinical response to treatment as evaluated by the study veterinarian, 97.2% of the marbofloxacin cases were reported as clinically cured or improved, as compared to 97.7% of the SDZ/TMP cases. Rates of elimination of the most common bacteria are provided in Table 5.

Table 5: Rates of elimination for individual pathogens of marbofloxacin treated dogs.

Pathogen	Number isolated pre-treatment	Number Eliminated	Percent Eliminated
<i>Escherichia coli</i>	23	23	100%
<i>Proteus mirabilis</i>	11	11	100%
<i>Staphylococcus intermedius</i>	4	4	100%
<i>Enterococcus faecalis</i>	2	1	50%
<i>Klebsiella pneumoniae</i>	2	2	100%
<i>Miscellaneous</i>	2	2	100%

More than one bacterial isolate may have been obtained from any given case.

Conclusions: Marbofloxacin administered orally at 1.25 mg/lb once daily for up to 14 days was safe and effective in the treatment of bacterial infections of the urinary tract (cystitis).

Suspected Adverse Drug Reactions: Clinical signs were noted in nine out of a total of 73 dogs treated with marbofloxacin (including both evaluable and non-evaluable cases), and may have been related to adverse reactions, although a causal relationship was not established. The following clinical signs were reported (number of cases in parenthesis): lethargy (5), vomiting (2), ataxia (1), decreased appetite (1), shaking (1), and soft stool (1).

## 2. Clinical Field Study - Canine Skin and Soft Tissue Infections Study Number MB-G-5000-94

Purpose: To demonstrate that marbofloxacin tablets administered at doses of 1.25 mg/lb and 2.5 mg/lb are safe and effective under clinical conditions for the treatment of skin and soft tissue infections in dogs.

Investigators:

Dr. R. Moffatt Ambler, PA	Dr. R. Brown Stuart, FL
Dr. W. Bender Granada Hills, CA	Dr. D. Rauch Mundelein, IL
Dr. J. Kinnarney Reidsville, NC	Dr. R. Benjamin Berkeley, CA
Dr. M. Frost Jacksonville, FL	Dr. M. Leven Grand Rapids, MI
Dr. J. Miller Granada Hills, CA	Dr. P. Davis Augusta, ME
Dr. E. Smith/Dr. N. DiMarco Juno Beach, FL	Dr. M. Tichacek/Dr. L. Gustavsen Lake Zurich, IL
Dr. J. Bacia Orlando, FL	Dr. R. McLain Addison, IL
Dr. L. Buzhardt Zachary, LA	Dr. L. Blackwell Grayslake, IL
Dr. B. Berryhill Baton Rouge, LA	Dr. S. Gluckman Mendon, NY
Dr. R. Gordon Oakland, NJ	

Animals: In order to participate in the studies, dogs had to have clinical evidence of skin or soft tissue infection. In order to continue in the study, confirmation of infection by bacterial culture and identification of the pathogen(s) was required. Of the 196 client-owned dogs initially enrolled in the study, 163 were evaluated for effectiveness, with 33 cases considered unevaluable. The most common causes that cases were deemed unevaluable were owner non-compliance in returning for post-treatment examinations, negative pre-treatment cultures, and complicating underlying diseases or medical conditions. Of the 163 evaluated cases, 50 cases were in the marbofloxacin 1.25 mg/lb group, 56 were in the marbofloxacin 2.5 mg/lb group and 57 were in the active control group. Forty-five various breeds were represented in the study, in addition to mixed breed dogs. Dogs ranged from 9 months to 16 years of age. Body weights ranged from 3.5 lb to 212 lb. Seventy-eight dogs were female and 85 were male.

Dosage Groups: Marbofloxacin 1.25 mg/lb  
Marbofloxacin 2.5 mg/lb  
Sulfadiazine/Trimethoprim (SDZ/TMP) 12.0 mg/lb

Dosage Forms: Marbofloxacin - proposed commercial formulation tablets  
SDZ/TMP - approved commercial tablets

Route of Administration: oral

Frequency of Treatment: Once daily for 5 to 14 days

Duration of Study: Maximum of 14 days, with post-treatment examination from 5 to 16 days later.

Pertinent Parameters Measured: Physical examination and lesion evaluation, bacteriological culture and susceptibility [minimum inhibitory concentration (MIC) determination], hematology, and blood chemistry panels were conducted. The study was conducted according to a blinded, controlled, randomized design.

Results: The primary parameter for determination of effectiveness was complete clinical resolution of the infection, which is summarized by treatment group in Table 6. The predominant pathogen was *Staphylococcus intermedius* (105 isolates), followed by *E. coli* (13 isolates) and numerous miscellaneous organisms. Evaluation of laboratory data revealed no clinically significant changes.

Table 6: Complete clinical resolution by treatment.

Treatment Group	Number Evaluated	Number Healed	Percent
Marbofloxacin 1.25 mg/lb	50	40	80.0 %
Marbofloxacin 2.5 mg/lb	56	43	76.8%
SDZ/TMP	57	47	82.5%

Conclusions: Marbofloxacin administered orally at either 1.25 mg/lb or 2.5 mg/lb once daily for a maximum of 14 days was safe and effective treatment for bacterial skin and soft tissue infections.

Suspected Adverse Drug Reactions: Clinical signs were noted which may have been related to adverse reactions, although causal relationship was not established. Of the 196 cases initially enrolled in the study, including the 33 cases considered unevaluable, 60 were in the marbofloxacin 1.25 mg/lb group and 71 were in the marbofloxacin 2.5 mg/lb group. Of the cases treated with 1.25 mg/lb of marbofloxacin, seven cases had a total of nine clinical signs which may have been related to drug therapy. Of the cases treated with 2.5 mg/lb of marbofloxacin, 14 cases had a total of 15 clinical signs possibly related to drug therapy. The following clinical signs were reported (number of cases in parenthesis): decreased appetite (8), vomiting (4), lethargy (4), anorexia (2), increased thirst (2), diarrhea (1), increased sexual aggressiveness (1), nervousness

(1). One dog which had a seizure the day before study enrollment experienced a seizure while on marbofloxacin therapy.

## V. ANIMAL SAFETY

### A. Drug Tolerance Study: Study MB-G-1005-94

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 a day for twelve days.

Investigator: Anthony L. Kiorpes  
Hazleton - Wisconsin, Inc.  
Madison, Wisconsin

Animals: Twelve beagle dogs 12.5 to 14 months of age, weighing 22.4 - 34.3 lb, 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 clinically effective dose)

Route of Administration: Oral

Frequency of Treatment: Once daily

Duration of Study: 12 days

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

Results: Treated dogs exhibited several clinical signs associated with overdose. These signs included vomiting, dehydration, tremors, excessive salivation, facial swelling, reddened skin, and decreased activity. Treated dogs had significantly less food consumption compared to the controls. Mean body weight loss over the course of the study for treated males was 12% of the Day 1 measurement. Treated females experienced a mean 20% weight loss over the course of the study. Grossly visible, focal, red areas of articular cartilage were seen in 2/6 placebo-treated dogs and in 4/6 marbofloxacin-treated dogs. The foci were areas of fibrocartilage with prominent vascularization or increased vascularization of subchondral bone. Due to the appearance microscopically and macroscopically, these red foci were described as likely to be developmental anomalies or normal variations in articular cartilage. No clinical lameness was noted in any dog.

Treatment was associated with mildly higher red blood cell count, hemoglobin, and hematocrit for males and females; mildly lower white blood cell count and absolute neutrophil count for males and females; mildly lower total protein and globulin for males; mildly higher alanine aminotransferase for males; and moderately lower sodium, potassium, and chloride for females.

Thymuses of all treated animals showed diffuse depletion of lymphocytes. Adrenal gland absolute and relative weights were increased for treated females, but histopathology showed no test article-related changes.

Conclusions: Administration of marbofloxacin at 25 mg/lb (10x the upper limit of the clinically effective dose) for 12 days was associated with markedly reduced food intake, vomiting, dehydration and sporadic erythema and/or facial swelling. Clinical laboratory variables influenced by treatment were mainly associated with dehydration and reduced food and/or water consumption. The clinical effects of overdose observed in this study were not associated with significant or irreversible pathology.

B. Safety Margin Study: MB-G-1004-94

Purpose: To evaluate the safety of marbofloxacin in dogs when administered at 1x, 3x, or 5x the upper limit of the clinically effective dosage for 6 weeks.

Investigator: Anthony L. Kiorpes  
Hazleton - Wisconsin, Inc.  
Madison, Wisconsin

Animals: Thirty-two beagle dogs 12 to 14 months of age, weighing 16.5 to 35.4 lb were randomly allocated to four 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 for 6 weeks

Duration of Study: 6 weeks

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

Analysis: Repeated measures analysis of variance was used to analyze food consumption, body weight, and clinical pathology variables. The baseline values were used as covariates in the repeated measures model. Organ weights were analyzed by analysis of variance. Treatments were compared to control at the 0.10 level. Sexes were analyzed together unless the sex by time or sex by treatment interaction was significant.

Results: Vomiting, reddened skin (usually involving the ears) and reddened mucous membranes were occasionally observed in all groups, including controls, but were noted most frequently in the 5x group. No clinical lameness was noted in any of the treated animals. Food consumption decreases were notable in the 3x and 5x treatment groups in the first week of treatment, but appetite increased thereafter, and were comparable to controls by the third week.

Dogs in the 3x and 5x treatment groups experienced significant weight losses of 4.8% and 7.7%, respectively, during the first week of treatment. After the first week of treatment, body weight changes for the treated groups were not remarkably different from corresponding control group values for the remainder of the study, as all groups had small weekly losses or gains.

Marbofloxacin treatment was associated with moderately lower serum total protein for animals in the 3x and 5x treatment groups. The change in total protein resulted from mild reductions in both albumin and globulin, with mean values remaining within normal limits.

No clinical lameness was noted in any of the treated animals. Minimal to slight lesions in the articular cartilage were observed in 1/8 placebo-treated animals and in 3/8 animals given the 5x dose. Macroscopically, these lesions were vesicles, raised areas or depressed, light-colored areas. Microscopically, these lesions were characterized by the presence of one or more of the following: fissuring, erosion, chondrocyte proliferation, fibrillation, or vertical splitting of the articular cartilage. These cartilage lesions in the treated dogs were similar to those in control dogs, and were not typical of those produced by fluoroquinolones. In addition to the above pathologic alterations, red areas of articular cartilage were noted macroscopically in 0/8 placebo-treated dogs and in 2/8 dogs from each of the three marbofloxacin-treated groups. These areas usually correlated microscopically with areas of vascularity of the articular surface, but could not be confirmed microscopically in all animals. They consisted of large blood vessels in mature fibrous connective tissue, with no indication of active vascularization due to drug-induced damage. They were considered most likely to be

developmental anomalies or normal variations of the joint surface and were not considered to be related to drug treatment.

Conclusions: Oral administration of marbofloxacin tablets to dogs at the maximum intended dose of 2.5 mg/lb produced no significant adverse reactions in young adult (12-14 month) beagle dogs.

C. Exploratory Safety Study in Young Large-Breed Dogs: MB-G-1001-94

Purpose: To examine the potential of marbofloxacin to induce arthropathy when administered to puppies during an active stage of growth at a dosage 2x the upper limit of the clinically effective dose of 2.5 mg/lb body weight, or 5 mg/lb.

Investigator: Dan W. Dalgard  
Hazleton Washington, Inc.  
Vienna, VA

Animals: Sixteen purpose-bred mongrel puppies 3 to 4 months of age, weighing 9.9 to 17.4 lb, were randomly allocated to two groups containing four males and four females each.

Dosage Groups: Placebo  
Marbofloxacin 5 mg/lb (2x the upper limit of the clinically effective dosage)

Route of Administration: Oral

Frequency of Treatment: Once daily for 14 days

Duration of Study: 14 days

Parameters Measured: Clinical observations, physical observations, food consumption and body weight, ophthalmic examination, neurological examination, and clinical, gross, and histopathology.

Results: Marbofloxacin treatment at the described dosage resulted in multiple articular cartilage lesions. There were no treatment-related clinical signs noted during Days 1 and 2. Evidence of lameness was noted in all treated dogs, with the first observations recorded on the third day in four dogs. Subsequent clinical observations including hunched posture, limited use of hind limbs, ataxia, decreased activity, decreased appetite and decreased fecal output were considered to be the result of discomfort associated with the lameness. At necropsy, macroscopic and microscopic lesions of the articular cartilage were observed in many of the diarthrodial joints examined. Lesions varied from vesicles to erosions and were characteristic of those produced by fluoroquinolone drugs.

Conclusions: Administration of marbofloxacin at 2x the upper limit of the clinically effective dosage to rapidly growing 3-4 month old mongrel puppies was not well tolerated due to articular cartilage lesions typical of those seen with fluoroquinolone antimicrobial agents.

## **VI. HUMAN SAFETY**

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in dogs 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 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 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 dogs, when used under labeled conditions of use, are safe and effective.

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 and urinary tract infections, management of the condition and monitoring of possible adverse effects of the drug.

Under section 512(c)(2)(F)(i) of the FDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

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