

AUG 1 2001

Zeniquin® (marbofloxacin) Tablets

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

NADA 141 - 151

Pfizer Inc.

NADA - 141-151

F05-1

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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.

Microorganism	n	Minimum Inhibitory Concentration (µg/mL)		
		MIC ₅₀	MIC ₉₀	Range
<i>Pasteurella multocida</i>	135	0.03	0.06	≤0.008 - 0.25
Beta-hemolytic <i>Streptococcus</i>	22	1	1	0.06 - 1
<i>Staphylococcus aureus</i>	21	0.25	0.5	0.125 - 1
<i>Corynebacterium</i> species	14	0.5	1	0.25 - 2
<i>Staphylococcus intermedius</i>	11	0.25	0.5	0.03 - 0.5
<i>Enterococcus faecalis</i>	10	2.0	2.0	1.0 - 2.0
<i>Escherichia coli</i>	10	0.03	0.03	0.015 - 0.03
<i>Bacillus</i> 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 \pm SD*		
	n=7		
AUC _{0 to inf} ($\mu\text{g}\cdot\text{h/mL}$)	70	\pm	6
C _{max} ($\mu\text{g/mL}$)	4.8	\pm	0.7
T _{max} (h)	1.2	\pm	0.6
t _{1/2 β} (h)	12.7	\pm	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

Zeniquin®

(marbofloxacin)

Tablets

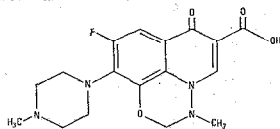
For oral use in dogs and cats only

CAUTION: 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.

DESCRIPTION: Marbofloxacin is a synthetic broad-spectrum antibacterial agent from the fluoroquinolone class of chemotherapeutic agents. Marbofloxacin is the non-proprietary designation for 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[3,2,1-ij][4,1,2] benzoxadiazine-6-carboxylic acid. The empirical formula is $C_{17}H_{19}FN_4O_4$ and the molecular weight is 362.36. The compound is soluble in water; however, solubility decreases in alkaline conditions. The N-octanol/water partition coefficient (Kow) is 0.835 measured at pH 7 and 25°C.

Figure 1: Chemical structure of marbofloxacin.



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

EFFECTIVENESS CONFIRMATION: Clinical effectiveness was confirmed in bacterial skin and soft tissue infections in dogs and cats and urinary tract infections (cystitis) in dogs associated with bacteria susceptible to marbofloxacin. Bacterial pathogens isolated in clinical field studies are provided in the **Microbiology** section.

DOSAGE AND ADMINISTRATION: The recommended dosage for oral administration to dogs and cats is 1.25 mg marbofloxacin per lb of body weight once daily, but the dosage may be safely increased to 2.5 mg/lb.

For the treatment of skin and soft tissue infections, Zeniquin tablets should be given for 2-3 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.

CLINICAL PHARMACOLOGY: Marbofloxacin is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration to fasted animals. Divalent cations are generally known to diminish the absorption of fluoroquinolones. The effects of concomitant feeding on the absorption of marbofloxacin have not been determined. (See **Drug Interactions**.) In the dog, approximately 40% of an oral dose of marbofloxacin is excreted unchanged in the urine. Excretion in the feces, also as unchanged drug, is the other major route of elimination in dogs. Ten to 15% of marbofloxacin is metabolized by the liver in dogs. *In vitro* plasma protein binding of marbofloxacin in dogs was 9.1% and in cats was 7.3%. In the cat, approximately 70% of an oral dose is excreted in the urine as marbofloxacin and metabolites with approximately 85% of the excreted material as unchanged drug. Pharmacokinetic parameters related to intravenous dosing were estimated in a study of 6 healthy adult beagle dogs, and are summarized in Table 1. The absolute bioavailability following dosing of oral tablets to the same animals was 94%.

Marbofloxacin plasma concentrations were determined over time in healthy adult beagle dogs (6 dogs per dosage group) following single oral doses of 1.25 mg/lb or 2.5 mg/lb. Absorption of orally administered marbofloxacin increases proportionally over the dose range of 1.25 to 2.5 mg/lb. Marbofloxacin plasma concentrations were determined over time in 7 healthy adult male cats following a single oral dose of 2.5 mg/lb. Plasma pharmacokinetic parameters following oral dosing of dogs and cats are summarized in Figures 2 and 3 and in Table 2. 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 25% greater in dogs and 35% greater in cats than those achieved after a single dose. Marbofloxacin is widely distributed in canine tissues. Tissue concentrations of marbofloxacin were determined in healthy male beagle dogs (4 dogs per time period) at 2, 18 and 24 hours after a single oral dose (1.25 or 2.5 mg/lb) and are summarized in Tables 3a and 3b.

Table 1: Mean pharmacokinetic parameters following intravenous administration of marbofloxacin to 6 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_{ss} (L/kg)	1.19 ± 0.08
$AUC_{0-\infty}$ (µg·h/mL)	59 ± 5
Terminal plasma elimination half-life, $t_{1/2}$ (h)	9.5 ± 0.7

* SD = standard deviation

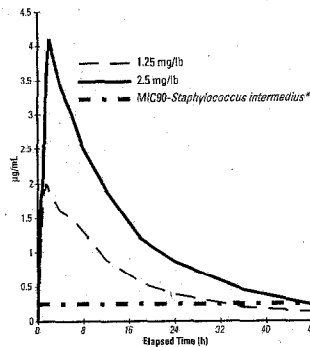
Table 2: Mean pharmacokinetic parameters following oral administration of marbofloxacin tablets to adult beagle dogs at a nominal dosage of 1.25 mg/lb or 2.5 mg/lb and to cats at 2.5 mg/lb.

Parameter	Dog Estimate ± SD* (1.25 mg/lb) n=6	Dog Estimate ± SD* (2.5 mg/lb) n=6	Cat Estimate ± SD* (2.5 mg/lb) n=7
Time of maximum concentration, T_{max} (h)	1.5 ± 0.3	1.8 ± 0.3	1.2 ± 0.6
Maximum concentration, C_{max} (µg/mL)	2.0 ± 0.2	4.2 ± 0.5	4.8 ± 0.7
$AUC_{0-\infty}$ (µg·h/mL)	31.2 ± 1.6	64 ± 9	70 ± 6
Terminal plasma elimination half-life, $t_{1/2}$ (h)	10.7 ± 1.6	10.9 ± 0.8	12.7 ± 1.1

* mean actual dosages administered to dogs were 1.22 mg/lb and 2.56 mg/lb, respectively, and the mean actual dosage administered to cats was 2.82 mg/lb.

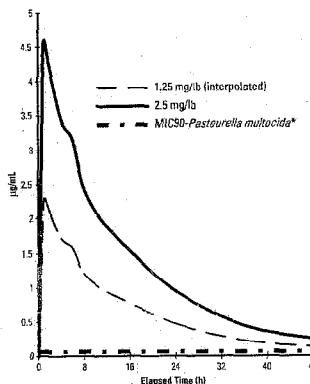
* SD = standard deviation

Figure 2: Mean plasma concentrations (µg/mL) following single oral administration of marbofloxacin to adult beagle dogs at dosages of 1.25 mg/lb or 2.5 mg/lb.



* See Table 4 in **Microbiology** section for MIC data.

Figure 3: Mean plasma concentrations (µg/mL) following single oral administration of marbofloxacin to adult cats at a dosage of 2.5 mg/lb.



* See Table 5 in **Microbiology** section for MIC data.

Table 3a: Tissue distribution following a single oral administration of marbofloxacin tablets to adult beagle dogs at a dosage of 1.25 mg/lb.

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

* SD = standard deviation

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

* SD = standard deviation

MICROBIOLOGY: The primary action of fluoroquinolones is to inhibit the bacterial enzyme, DNA gyrase. In susceptible organisms, fluoroquinolones are rapidly bactericidal at relatively low concentrations. Marbofloxacin is bactericidal against a broad range of gram-negative and gram-positive organisms. The minimum inhibitory concentrations (MICs) of pathogens isolated in clinical field studies performed in the United States were determined using National Committee for Clinical Laboratory Standards (NCCLS) standards, and are shown in Tables 4 and 5.

		Project Name	
		Zeniquin Cats Fac	
PACKAGE DESIGN & DEVELOPMENT		Project Number	
Animal Health		1893	
Editor	Michele Brettmann		
Coordinator	Penny Rousseau		
Artist	Amy French		
Proofreader	Diane Mattison		
Part Number	Draft#	Date	
75-8485-X1	1	19APR01	
Dimensions: 7 3/4" (W) x 14" (H)			
Folds to: 1" x 2"			
Code(s) 12 of 5 Code: 031(4)			
Colors: Visual Code Bars: 1, 2			
		SKU: 8485000	

Table 4: MIC Values* ($\mu\text{g/mL}$) of marbofloxacin against pathogens isolated from skin, soft tissue and urinary tract infections in dogs enrolled in clinical studies conducted during 1994–1996.

Organism	No. of Isolates	MIC ₅₀	MIC ₉₀	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	≤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> spp.	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.

** MIC₅₀ and MIC₉₀ not calculated due to insufficient number of isolates.

Table 5: MIC Values* ($\mu\text{g/mL}$) of marbofloxacin against pathogens isolated from skin and soft tissue infections in cats enrolled in clinical studies conducted in 1995 and 1998.

Organism	No. of Isolates	MIC ₅₀	MIC ₉₀	MIC Range
<i>Pasteurella multocida</i>	135	0.03	0.06	≤0.008–0.25
Beta-hemolytic <i>Streptococcus</i>	22	1	1	0.06–1
<i>Staphylococcus aureus</i>	21	0.25	0.5	0.125–1
<i>Corynebacterium</i> spp.	14	0.5	1	0.25–2
<i>Staphylococcus intermedius</i>	11	0.25	0.5	0.03–0.5
<i>Enterococcus faecalis</i>	10	2.0	2.0	1.0–2.0
<i>Escherichia coli</i>	10	0.03	0.03	0.015–0.03
<i>Bacillus</i> spp.	10	0.25	0.25	0.125–0.25

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

DRUG INTERACTIONS: Compounds (e.g., sucralfate, antacids, and mineral supplements) containing divalent and trivalent cations (e.g., iron, aluminum, calcium, magnesium, and zinc) can interfere with the absorption of quinolones which may result in a decrease in product bioavailability. Therefore, the concomitant oral administration of quinolones with foods, supplements, or other preparations containing these compounds should be avoided.

CONTRAINDICATIONS: Marbofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested, the dog being particularly sensitive to this side effect. Marbofloxacin is contraindicated in immature dogs during the rapid growth phase (small and medium breeds up to 8 months of age, large breeds up to 12 months of age and giant breeds up to 18 months of age). Marbofloxacin is contraindicated in cats under 12 months of age. Marbofloxacin is contraindicated in dogs and cats known to be hypersensitive to quinolones.

PRECAUTIONS: Quinolones should be used with caution in animals with known or suspected central nervous system (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures. Quinolones have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. The use of fluorquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats. The safety of marbofloxacin in animals used for breeding purposes, pregnant, or lactating has not been demonstrated.

HUMAN WARNING: 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 fluorquinolones 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.

TARGET ANIMAL SAFETY:

Dogs: The toxicity of marbofloxacin was assessed in 12- to 14-month-old beagle dogs administered marbofloxacin at 2.5, 7.5 and 12.5 mg/lb/day for 42 days. 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 12.5 mg/lb group. Decreased food consumption and weight loss were significant in the 7.5 mg/lb and 12.5 mg/lb groups. 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 12.5 mg marbofloxacin/lb. 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 treated dogs were similar to those in control dogs, and were not typical of those produced by fluorquinolones. 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.

Marbofloxacin was administered to 12- to 14-month-old beagle dogs at a dosage of 25 mg/lb/day for 12 days. Decreased food consumption, vomiting, dehydration, excessive salivation, tremors, reddened skin, facial swelling, decreased activity

and weight loss were seen in treated dogs. No clinical lameness was noted. As in the 42 day study, grossly visible, focal, red areas of articular cartilage were seen. These findings were noted 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.

Marbofloxacin administered to 3- to 4-month-old, large breed, purpose-bred mongrel dogs at a dosage of 5 mg/lb/day for 14 days resulted in marked lameness in all dogs due to articular cartilage lesions. Lameness was accompanied by decreased appetite and activity.

Cats: Marbofloxacin was administered for 42 consecutive days to 24 cats approximately 8 months old (8 cats per treatment group) at the dosages of 2.5, 7.5 and 12.5 mg/lb/day (5.5, 16.5 and 27.5 mg/kg/day). Treatment with marbofloxacin did not produce adverse effects on body weights, food consumption, serum chemistry, urinalysis or organ weight parameters. Decreased segmented neutrophil counts were observed in some cats in all treatment groups, including the placebo group, but mean counts were significantly lower in the marbofloxacin-treated groups. In some cats, absolute neutrophil counts were below normal reference values (as low as 615 neutrophils/ μL in a marbofloxacin-treated cat and as low as 882 neutrophils/ μL in a placebo-treated cat). Other hematological observations were not adversely affected. Clinical signs were occasionally noted in cats in the highest dosage group: excessive salivation in 4/8 cats and redness of ear pinnae in 2/8 cats. Macroscopic changes in the articular cartilage of femurs were seen in one cat receiving 7.5 mg/lb and in 3 cats receiving 12.5 mg/lb. Microscopically, these gross lesions were related to a focal or multifocal chondropathy. Microscopic chondropathy not associated with macroscopic observations was also present in one cat treated with 2.5 mg/lb daily (1X the upper end of the dose range) and one additional cat treated with 7.5 mg/lb daily. There was no evidence of lameness during the course of the study. A perivascular to diffuse dermatitis was seen microscopically in one mid-dose cat and 4 high-dose cats. Funduscopic exam by a board-certified ophthalmologist and histologic examination of retina and optic nerve by ocular pathologists revealed no lesions in any of the treatment groups.

Marbofloxacin was also administered orally to 6 cats approximately 8 months of age for 14 consecutive days at a dosage of 25 mg/lb/day (55 mg/kg/day). Clinical signs associated with drug intolerance were excessive salivation in 5/6 cats and redness of ear pinnae in all cats after 8 days of treatment. Emesis was noted occasionally in several cats and diminished activity was noted in one cat. Decreased food intake was noted in some animals, primarily males, when compared to controls. Perivascular to diffuse dermatitis was seen microscopically in the pinnae of all treated animals and in the standard skin samples of several animals. There was focal or multifocal articular chondropathy in 2/6 treated animals. One treated cat had a duodenal mucosal erosion and one treated cat had a pyloric ulcer. There were no observations of lameness and no adverse effects on hematology, clinical chemistry, urinalysis, or organ weight parameters. Funduscopic examination by a board-certified ophthalmologist and histologic examination of retina and optic nerve by ocular pathologists revealed no lesions.

A study was conducted to investigate the effect of marbofloxacin on articular cartilage of skeletally mature cats 12–14 months of age. Forty cats were randomly assigned to 4 groups of 10 cats each. Groups received placebo or marbofloxacin at dosages of 1.25, 3.75 or 7.5 mg/lb/day (2.75, 8.25 or 16.5 mg/kg/day) for 42 consecutive days. There were no treatment-related pathological changes in the joints or other tissues. Emesis and soft stools was noted in all treatment groups, including placebo, and increased in frequency with increasing dose and duration of treatment. Emesis was more apparent in the high-dose males.

ADVERSE REACTIONS: The following clinical signs were reported during the course of clinical field studies in dogs receiving marbofloxacin at dosages up to 2.5 mg/lb daily: decreased or loss of appetite (5.4%), decreased activity (4.4%), and vomiting (2.9%). The following signs were reported in less than 1% of cases in dogs: increased thirst, soft stool/diarrhea, behavioral changes, shivering/shaking/tremors, and ataxia. One dog which had a seizure the day before study enrollment experienced a seizure while on marbofloxacin therapy.

The following clinical signs were reported during clinical field studies in cats receiving 1.25 mg/lb/day: diarrhea (2.1%) and soft stool (1.4%). Vomiting was reported in less than 1% of cases in cats.

HOW SUPPLIED: Marbofloxacin is supplied in 25-mg, 50-mg, 100-mg, and 200-mg scored, coated tablets.

STORAGE CONDITIONS: Store below 30°C (86°F).

REFERENCES:

1. Schneider M, et al: Pharmacokinetics of marbofloxacin in dogs after oral and parenteral administration. *J Vet Pharmacol Therap* 19:56–61, 1996.

To report suspected adverse effects, and/or obtain a copy of the MSDS, call 1-800-366-5288.

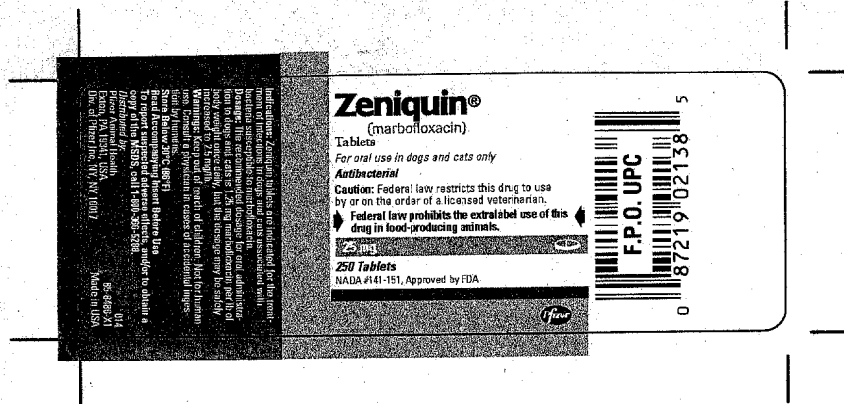
NADA 141-151, Approved by FDA






Distributed by:



Animal Health

Exton, PA 19341, USA
Div. of Pfizer Inc
NY, NY 10017



 PACKAGE DESIGN & DEVELOPMENT Animal Health	Project Name	Part Number	Draft#	Date	Dimensions
	Zeniquin Cats Facsimile	85-8486-X1	1	16APR01	1 3/8" x 3 3/4"
	Project Number	Country	Visual Code Bar(s)		
	1893	USA			
		Die (CAD)#	Code(s) UPC		
Editor	Michele Brettmann	Colors:			
Coordinator	Penny Rousseau				
Artist	Amy French	PMS 116	PMS 131	PMS 3155	PMS 425
Proofreader	Diane Mattison				Black
SKU: 8486000					

SKU: 8486000

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Zeniquin®

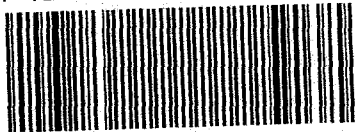
(marbofloxacin)

8485

25 mg Tablets

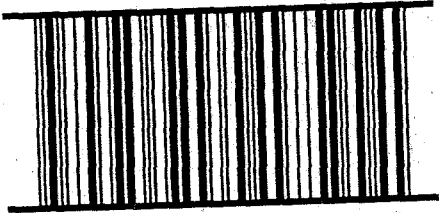
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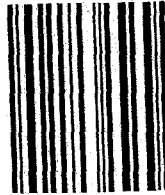


22 900072 ??? ???? 1

Store below
30°C(86°F)



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0072



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Zeniquin[®]

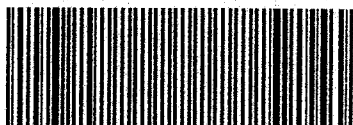
(marbofloxacin)

8486

25 mg Tablets

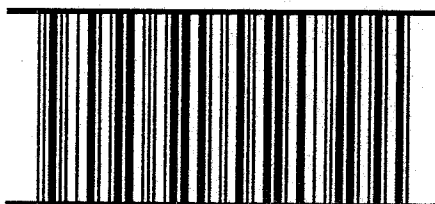
24 250-tablet bottles

QTY 24 EXP ??/?? LOT ???????



22 900024 ??? ? ????? 2

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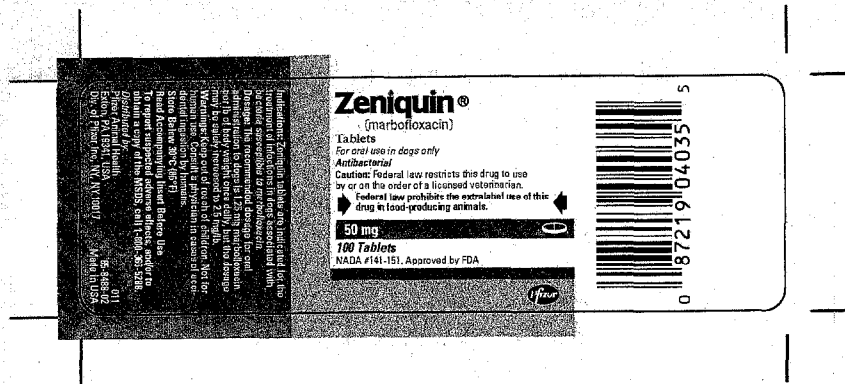








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0024





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	Zeniquin	85-8488-02	15JAN01	1 1/4" (H) x 3 3/4" (W)		
	Project Number	Country US	Visual Code Bar(s)			
	1605	Die (CAD)#	Code(s) UPC			
		Colors:				
Editor	Michele Brettmann					
Coordinator	Penny Rousseau	PMS 116	PMS 286	PMS 3155	PMS 425	Black
Artist	Ron VanValkenburg					
Proofreader	Diane Mattison					



Indications: Zeniquin tablets are indicated for the treatment of infections in dogs associated with bacteria susceptible to marbofloxacin.

Dosage: The recommended dosage for oral administration to dogs is 1.25 mg marbofloxacin per lb of body weight once daily, but the dosage may be safely increased to 2.5 mg/lb.

Warnings: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans.

Store Below 30°C (86°F).

Read Accompanying Insert Before Use.

To report suspected adverse effects, and/or to obtain a copy of the MSDS, call 1-800-366-8288.

Zeniquin®

(marbofloxacin)

Tablets

For oral use in dogs only

Antibacterial

Caution: 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.

50 mg


250 Tablets

NADA #141-151, Approved by FDA

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Exton, PA 19341, USA
Div. of Pfizer Inc.
NY, NY 10017

011
85-8489-02
Made in USA

87219 02142 2

 CENTRAL LABELING SERVICES	Project Name	Part Number	Date	Dimensions
	Zeniquin	85-8489-02	15JAN01	2 1/2" (H) x 4 1/4" (W)
	Project Number	Country	US	Visual Code Bar(s)
	1605	Die (CAD)#		Code(s) UPC
Editor	Michele Brettmann	Colors:		
Coordinator	Penny Rousseau			
Artist	Ron VanValkenburg	PMS 116	PMS 286	PMS 3155
Proofreader	Diane Mattison		PMS 425	Black



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Zeniquin®

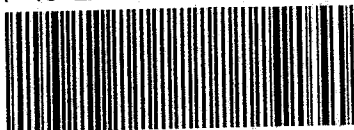
(marbofloxacin)

8488

50 mg Tablets

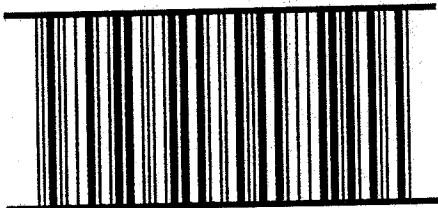
48 100-tablet bottles

QTY 48 EXP ??/?? LOT ???????



22 900048 ???? ??????? 2

Store below
30°C(86°F)



1 00 87219 04035 2



0048



DIST. BY: PFIZER ANIMAL HEALTH, EXTON, PA 19341, USA
DIV. OF PFIZER INC, NY, NY 10017

8489

Zeniquin®
(marbofloxacin)
50 mg Tablets

12 250-tablet bottles

QTY 12 EXP ??/?? LOT ???????



22 900012 ??? ???? 9

Store below
30°C(86°F)



0000

1 00 87219 02142 9

MADE IN USA



0012 CL-8489-01

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DIV. OF PFIZER INC, NY, NY 10017

8489

Zeniquin®
(marbofloxacin)
50 mg Tablets

12 250-tablet bottles

QTY 12 EXP ??/?? LOT ???????



22 900012 ??? ???? 9

Store below
30°C(86°F)

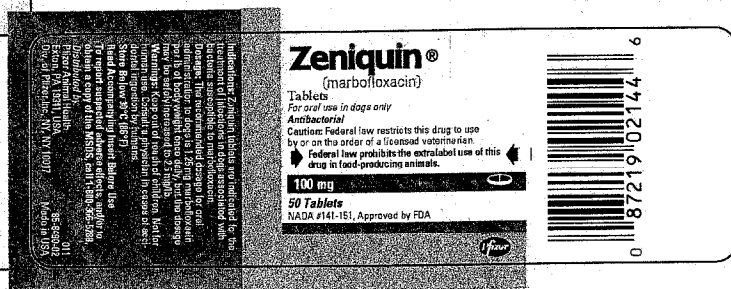








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0012





 CENTRAL LABELING SERVICES	Project Name	Part Number	Date	Dimensions		
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	Project Number	Country US		Visual Code Bar(s)		
	1605	Die (CAD)#		Code(s) UPC		
	Editor	Michele Brettmann	Colors:			
Coordinator	Penny Rousseau					
Artist	Ron VanValkenburg	PMS 116	PMS Rhodamine Red	PMS 3155	PMS 425	Black
Proofreader	Diane Mattison					



DIST. BY: PFIZER ANIMAL HEALTH, EXTON, PA 19341, USA
DIV. OF PFIZER INC, NY, NY 10017

Zeniquin[®]

(marbofloxacin)

8490

100 mg Tablets

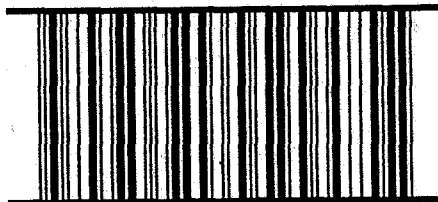
48 50-tablet bottles

QTY 48 EXP ??/?? LOT ???????

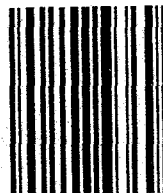


22 900048 ???? ??????? 3

Store below
30°C(86°F)



1 00 87219 02144 3



0048



Indications: Zeniquin tablets are indicated for the treatment of infections in dogs associated with bacteria susceptible to marbofloxacin.

Dosage: The recommended dosage for oral administration to dogs is 1.25 mg marbofloxacin per lb of body weight once daily, but the dosage may be safely increased to 2.5 mg/lb.

Warnings: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans.

Store below 20°C (68°F).

Read Accompanying Insert Before Use.

To report suspected adverse effects, and/or to obtain a copy of the MSDS, call 1-800-365-5288.

Zeniquin®

(marbofloxacin)

Tablets

For oral use in dogs only

Antibacterial

Caution: 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.

200 mg

50 Tablets






NADA #141-151, Approved by FDA

011
85-8494-02
Made in USA

Distributed by:
Pfizer Animal Health
Exton, PA 19341, USA
Div. of Pfizer Inc
NY, NY 10017



0 87219 02150 7

 CENTRAL LABELING SERVICES	Project Name	Part Number	Date	Dimensions	
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	Project Number	Country	Visual Code Bar(s)		
	1605	US			
		Die (CAD)#	Code(s) UPC		
Editor	Michele Brettmann	Colors:			
Coordinator	Penny Rousseau				
Artist	Ron VanValkenburg	PMS 116	PMS 3275	PMS 3155	PMS 425
Proofreader	Diane Mattison				Black



DIST. BY: PFIZER ANIMAL HEALTH, EXTON, PA 19341, USA
DIV. OF PFIZER INC., NY, NY 10017

8494

Zeniquin®
(marbofloxacin)
200 mg Tablets

12 50-tablet bottles

QTY 12 EXP ??/?? LOT ??????



22 900012 ??? ???? 4

Store below
30°C (86°F)



0000 1 00 87219 02150 4

MADE IN USA



0012 CL-8494-01

DIST. BY: PFIZER ANIMAL HEALTH, EXTON, PA 19341, USA
DIV. OF PFIZER INC., NY, NY 10017

8494

Zeniquin®
(marbofloxacin)
200 mg Tablets

12 50-tablet bottles

QTY 12 EXP ??/?? LOT ??????

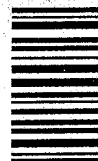


22 900012 ??? ???? 4

Store below
30°C (86°F)



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0012

