CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

PHARMACOLOGY REVIEW

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This application is approvable from a nonclinical perspective with some minor modifications of labeling as revised in the "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy", and "Animal and in vitro Pharmacology" sections.

B. Recommendation for Nonclinical Studies

No recommendation is necessary.

C. Recommendations on Labeling

Minor modifications of labeling in the "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy", and "Animal and in vitro Pharmacology" sections (see Labeling Review) are recommended.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Following topical ocular administration to rabbits, gatifloxacin was rapidly absorbed and well distributed in the eye. The systemic exposure to the drug following ocular administration in dogs and rabbits was very low. Pharmacology studies showed the drug is effective in reducing the severity of corneal infections. No biologically significant toxic effects were observed in ocular toxicity studies.

B. Pharmacologic Activity

Gatifloxacin is a synthetic broad spectrum, 8-methoxy fluoroquinolone antibacterial agent. Fluoroquinolones are known to work by inhibiting the interaction of DNA gyrase and topoisomerase IV with DNA, thus preventing bacterial replication. As a C8-methoxy derivative, gatifloxacin appears to have enhanced antibacterial activity, reduced phototoxicity and less resistant mutants of gram-positive bacteria compared to the non-methoxy C8 moiety.

The results from 3 in vivo efficacy studies suggested that topically applied gatifloxacin (0.1%, 0.3% and 0.5%) was equal or more effective than ofloxacin 0.3% and ciprofloxacin 0.3% ophthalmic solutions in treating both MRSA (methicillin-resistant *Staphylococcus aureus*)-induced keratoconjunctivitis and *Pseudomonas aeruginosa*-induced keratitis corneal ulceration model in rabbits. The optimal efficacious concentration was estimated to be 0.3%

C. Nonclinical Safety Issues Relevant to Clinical Use

Gatifloxacin ophthalmic solution at the concentrations up to 0.5% was well tolerated. The drug showed a very low ocular irritation potential. No toxicologically significant side effects were noted.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
NDA 21-493/Division File
NDA 21-493/Original NDA
HFD-550/CSO/Gorski
HFD-550/MO/Harris
HFD-550/TL Pharm/Yang
HFD-550/Pharm/ChenZ

APPEARS THIS WAY ON ORIGINAL

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PHARMACOLOGY/TOXICOLOGY REVIEW

Reviewer's Comments: Gatifloxacin has been approved for oral and intravenous administrations in December 1999. A comprehensive package of nonclinical studies was performed by Bristol-Myers Squibb and reviewed by Dr. Amy L Ellis (HFD-520) under NDA 21-061 and NDA 21-062. Please refer to *the Review and Evaluation of pharmacology and toxicology Data* for NDA 21-061 and NDA 21-062 for specific nonclinical studies. In this NDA review, only new studies and studies related to the ophthalmic administration are reviewed.

I. PHARMACOLOGY:

Studies reviewed:

Efficacy of Gatifloxacin Ophthalmic Solution on MRSA Ocular Infection in Rabbits (Senju report no. 4990303)
Dose-Dependent Efficacy of Gatifloxacin Ophthalmic Solution and Comparison of Efficacy with 0.3% Ofloxacin Ophthalmic Solution on MRSA Ocular Infection in Rabbits (Senju report no. 4990304)
Gatifloxacin Ophthalmic Solution: A Corneal Healing Study of *Pseudomonas Keratitis* in Rabbits (Allergan study no. TX00046)
Gatifloxacin: In Vitro Wound Closure Evaluation of Quinolone Antibiotics Using Rabbit Corneal Epithelial Cells (Allergan Study no. TX02022)

Efficacy of Gatifloxacin Ophthalmic Solution on MRSA Ocular Infection in Rabbits (Senju report no. 4990303). Vol. 10, Page 96.

Testing facility: Research Laboratories, Senju Pharmaceutical Co., Ltd., Japan
Report Dated: March 25, 1999

The efficacy of gatifloxacin against ocular infection with methicillin-resistant *Staphylococcus aureus* (MRSA) was compared with that of ofloxacin in male Japanese white rabbits. Ocular infection was induced by injection of MRSA suspension (5×10^5 CFU/ml, 30 µl) into the corneal stroma using a microsyringe. The drug (gatifloxacin 0.5%, ofloxacin 0.3% or saline, 5 eyes/group) was administered topically at 5, 12, 20, and 28 hours after the bacterial inoculation. Ocular infection signs were observed macroscopically at 8, 16, 24, 32, 48, and 72 hours post-inoculation, using a rating scale that included evaluation of the cornea, conjunctiva, discharge, iris, and hypopyon. The ocular infectious signs in saline-treated animals reached a maximum at 24 hr after inoculation, and gradually decreased. Both gatifloxacin and ofloxacin significantly reduced the signs of infection beginning at 16 hr and continued through the duration of the study (see table below).

Effects of 0.5% gatifloxacin and 0.3 ofloxacin on rabbit ocular infection (mean ± SE)

Infectious score		Time after inoculation (hr)					
Treatment	N	8	16	24	32	48	72
Saline	5	9.0 ± 0.5	21.7 ± 1.7	25.9 ± 1.7	24.5 ± 1.7	22.7 ± 1.0	20.3 ± 1.5
0.3% ofloxacin	5	7.1 ± 1.3	13.0 ± 2.8	13.2 ± 3.6	12.6 ± 3.3	8.0 ± 3.4	4.3 ± 2.8
0.5% gatifloxacin	5	7.0 ± 0.4	9.6 ± 0.5	11.8 ± 2.0	6.6 ± 1.6	1.7 ± 1.1	1.6 ± 1.1

Dose-Dependent Efficacy of Gatifloxacin Ophthalmic Solution and Comparison of Efficacy with 0.3% Ofloxacin Ophthalmic Solution on MRSA Ocular Infection in Rabbits (Senju report no. 4990304). Vol. 10, Page 107.

Testing facility: Research Laboratories, Senju Pharmaceutical Co., Ltd., Japan
Report Dated: March 25, 1999

A dose-ranging evaluation of gatifloxacin 0.02%, 0.1%, 0.3% and 0.5%, and ofloxacin 0.3%, was conducted in the male Japanese white rabbit MRSA model. The corneal stroma was inoculated with an MRSA solution (9.3 x 10^3 CFU/ml, 30 µl) and 50 µl of drug was dosed topically (7-8 eyes/group) at 5 and 24 hours post-inoculation. The efficacy parameters were anterior segment signs, bacterial viability and histopathological findings. Ocular infection (mild haze at the center of the cornea, marked scar of bacterial inoculation, marked vasodilatation, and edema) in the saline-treated groups peaked at 16 hr and slightly decreased but remained high through the 48 hr observation period. Gatifloxacin, starting at 16 hr after infection, decreased the scores of ocular infection in a dose-dependent fashion. This inhibitory effect was significant at 16 hr at 0.1%, 0.3% and 0.5%, up to 32 hr in the 0.1% group, and up to 48 hr in the 0.3% and 0.5% groups. The efficacy of 0.3% and 0.5% gatifloxacin was similar. The antibacterial effect of ofloxacin was approximately equal to 0.1% gatifloxacin, inferior to 0.3% and 0.5% gatifloxacin, and was not significant at 24 hr or beyond. Viable bacterial counts in corneal tissue were obtained at 52 hr after the infection. A reduction in viable bacteria was noted in all gatifloxacin groups in a dose-dependent manner, and all concentrations were more effective than ofloxacin. Histopathological examination of the eye was completed at 52 hr post-infection. Several abnormalities (presence of Gram-positive bacterial colonies, abscess formation, swelling of the corneal stromal layer, infiltration of inflammatory cells into various ocular tissues) were observed in the saline-treated group. These were distinctly alleviated in the 0.3% and 0.5% gatifloxacin groups and in the ofloxacin group. The ocular infection scores, AUC of the scores, and inhibitory rates are summarized in the table below. In conclusion, gatifloxacin showed dose-dependent efficacy in suppressing the development of signs of infection, corneal viable bacterial counts, and severity of histopathological findings in the rabbit MRSA model. The optimal concentration was estimated to be 0.3%.

Summary of rabbit ocular infection data

Infectious score		Time after inoculation (hr)					AUC_{0-48} hr	Inhibitory rate (%)
Treatment	N	8	16	24	32	48		
Saline	7	8.0 ± 0.9	18.9± 1.8	18.1 ± 2.8	17.2± 2.5	16.7± 2.8	564.3± 56.9	
0.3% ofloxacin	7	7.3 ± 0.8	11.6± 1.4**	13.3± 2.5	12.3± 3.3	12.1± 3.7	404.9± 67.3	28.3± 11.9
0.02% gatifloxacin	7	9.9 ± 0.9	14.3± 1.7	16.0± 1.7	15.0± 2.2	13.8± 2.6	496.9± 47.7	11.9± 8.4
0.1% gatifloxacin	7	6.6 ± 0.8	9.9± 1.7***	11.2± 2.1*	10.4± 2.3	9.0± 2.6	340.6± 52.3	39.6± 9.3
0.3% gatifloxacin	7	5.9 ± 1.0	9.2± 1.5***	9.2± 0.9**	7.5± 0.7**	6.4± 1.3	280.3± 20.2	50.3± 3.6
0.5% gatifloxacin	8	6.3 ± 0.5	8.2± 1.1***	8.5± 1.1***	7.4± 0.7***	3.8± 0.7	258.5± 15.6	54.2± 2.8

* p<0.05; ** p<0.01; *** p<0.001

Gatifloxacin Ophthalmic Solution: A Corneal Healing Study of *Pseudomonas Keratitis* in Rabbits (Allergan study no. TX00046). Vol. 10, Page 125.

Testing facility: —

Report Dated: December 3, 2001

The purpose of this study was to evaluate the effects of various treatment regimens (see table below) using gatifloxacin 0.3% ophthalmic solution on corneal healing in an heptanol-induced corneal ulceration model of *Pseudomonas* keratitis in female New Zealand white rabbits.

Dosing regimens

Group	Treatment	Study day	Dosing frequency/day
1	0.3% ciprofloxacin	2	44 (every 15 min for 6 hr, then 30 min for 10 hr)
		3	16 (every hr for 16 hr)
		4-22	4 (every 4 hr for 16 hr)
2	0.3% gatifloxacin	2-3	16 (every hr for 16 hr)
		4-22	4 (every 4 hr for 16 hr)
3	0.3% gatifloxacin	2	48 (every 15 min for 8 hr, then 30 min for 8 hr)
		3	16 (every hr for 16 hr)
		4-22	3 (16 hr period)
4	0.3% gatifloxacin	2	48 (every 15 min for 8 hr, then 30 min for 8 hr)
		3	16 (every hr for 16 hr)
		4-22	4 (every 4 hr for 16 hr)
5	0.3% gatifloxacin	2-3	32 (every 30 min for 16 hr)
		4-8	16 (every hr for 16 hr)
		9-22	4 (every 4 hr for 16 hr)

A topical application of heptanol created a 6.5 mm ulcer on the right eye of each rabbit (8 rabbits/group). The eye was then inoculated with — *Pseudomonas aeruginosa*. The signs of keratitis were produced within 24 hr after inoculation. The first instillation of drug was at 24 hours post-inoculation and the study lasted 23 days. The followings were evaluated: mortality, clinical observations, corneal infection scores, fluorescein retention scores, ophthalmologic examinations, and conjunctival cultures. The results showed that all parameters were consistent with an improvement of the infection over the course of the study. All conjunctival cultures were negative for *Pseudomonas aeruginosa* by the end of the study. There were no differences in efficacy among the four regimens of gatifloxacin treatment and ciprofloxacin treatment. In conclusion, administration of gatifloxacin 0.3%, at any of the 4 dosing regimens, was as effective as ciprofloxacin 0.3% under the conditions of this study.

Gatifloxacin: *In Vitro* Wound Closure Evaluation of Quinolone Antibiotics Using Rabbit Corneal Epithelial Cells (Allergan Study no. TX02022) Vol. 10, Page 205.

Testing facility: Allergan, 2525 Dupont Drive, Irvine, CA 92612
Report Dated: April 19, 2002

The purpose of this study was to evaluate the relative effects of quinolone antibiotics on *in vitro* wound closure in rabbit corneal epithelial cells. Five quinolone antimicrobial agents (gatifloxacin, ofloxacin, ciprofloxacin, moxifloxacin and levofloxacin) were used to treat primary cultures of rabbit corneal epithelial cells. One 12-well tissue culture plate was used for each quinolone and consisted of triplicate wells of each: control, 0.2, 0.4 and 0.6 mM quinolone. Prior to treatment, a 6-7 mm circular defect or "wound" was made in the center of confluent epithelial cell sheets with a cotton swab. Cultures were treated with quinolones at concentrations of 0.2, 0.4 or 0.6 mM at 37 °C. Digital images of wounds were taken at the initiation of treatment and 13, 22, 38, 45, and 64 hr thereafter, in order to determine the areas of the wounds.

Wounds in control cultures without quinolones closed rapidly, within 38 hr. Quinolones caused a dose-dependent inhibition of the wound closure rate. The 0.2 mM concentration caused little or no inhibition of wound closure. The differences between quinolones were most evident at 0.4 and 0.6 mM concentrations. Ciprofloxacin at 0.4 and 0.6 mM and moxifloxacin at 0.6 mM caused almost complete inhibition of wound closure. In conclusion, quinolone of different structures at equivalent molar concentrations caused different degrees of inhibition of *in vitro* wound closure rates in rabbit corneal epithelial cells. The wound closure rate showed the following rank order: untreated ≥ofloxacin ≥ levofloxacin > gatifloxacin > moxifloxacin > ciprofloxacin.

Pharmacology summary and conclusions:

The results from 3 *in vivo* efficacy studies suggested that topically applied gatifloxacin (0.1%, 0.3% and 0.5%) was equal or more effective than 0.3% ofloxacin and 0.3% ciprofloxacin ophthalmic solutions in treating both MRSA-induced keratoconjunctivitis and *Pseudomonas aeruginosa*-induced keratitis corneal ulceration model in rabbits. The optimal efficacious concentration was estimated to be 0.3%.

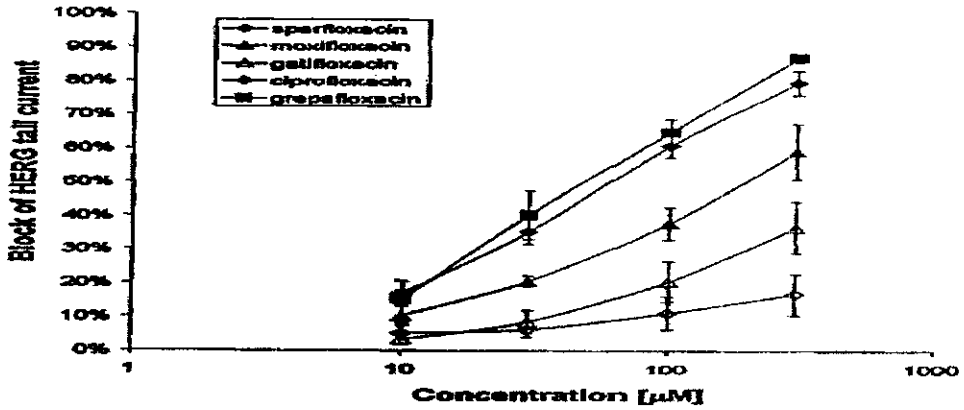
II. SAFETY PHARMACOLOGY:

Studies reviewed:

Effects of Gatifloxacin and Other Quinolones on HERG (Ikr) Currents (BMS Study no. 92002291)

Effects of Gatifloxacin and Other Quinolones on HERG (Ikr) Currents (BMS Study no. 92002291). Vol. 10, Page 193.

The human ether-a-go-go related gene (HERG) encodes the rapidly delayed-rectifier potassium channel (Ikr) in heart. Drugs that inhibit HERG/Ikr can induce excessive prolongation of the QT interval. The purpose of this *in vitro* study was to determine the effects of 5 different quinolones (sparfloxacin, grepafloxacin, moxifloxacin, gatifloxacin and ciprofloxacin) on HERG since some drugs in this class can prolong QT interval in humans. Human embryonic kidney (HEK293) cells were transfected with HERG cDNA. The HERG-expressing cells were used in conjunction with voltage-clamp techniques to test the drugs for HERG current inhibition. The concentrations of the drugs used in this study were 10, 30, 100 and 300 μM. The results showed that gatifloxacin was a weak inhibitor of the Ikr channel with no inhibition at concentrations up to 30 μM, which was 3- to 4-fold the human blood mean Cmax levels following clinical oral or intravenous dosing. The degree of inhibition by gatifloxacin compared to the fluoroquinolones tested was slightly more than ciprofloxacin, slightly less than moxifloxacin, and substantially less than grepafloxacin or sparfloxacin.



Effects of Gatifloxacin and Other Quinolones on HERG (Ikr) Currents. BMS Report 920002291

III. PHARMACOKINETICS/TOXICOKINETICS:

Toxicokinetic Analysis for Study No. TX00065 Entitled "Gatifloxacin (AGN198172): a 1- and 3-Month Ocular Toxicity Study in Dogs" (PK Report no. PK-01-061) Vol. 11, Page 239.

Key study findings:

Following repeat topical ocular administrations of 0.5% gatifloxacin ophthalmic solution to dogs, gatifloxacin was systemically absorbed
Testing facility:

Report dated: September 17, 2001

In a 1- and 3-month ocular toxicity study, male and female beagle dogs (6/sex/group) were topically dosed with 0% (placebo) and 0.5% gatifloxacin ophthalmic solutions for 1 and 3 consecutive months. One group of dogs received two drops (approximately 80 µl) of 0.5% gatifloxacin ophthalmic solution 10 times daily to the right eye (30 min between doses) for one month. A separate group of dogs received two drops (approximately 80 µl) of 0.5% gatifloxacin solution to the right eye 32 times daily (30 min between doses) for 2 days, 16 times daily (30 min between doses) for 5 days, and followed by 4 times daily (2 hr between doses) for the remainder of the 3 months. On days 7 and 28 in the 1-month treatment group, blood samples were collected from each dog before the 1st, 3rd, 7th, and 10th dose and at 0.5, 1, 2, 4, 8, and 12 hr following the last dose. In the 3-month treatment group, blood samples were collected before the 1st, 5th, 13th, 25th, and 32nd dose and at 0.5, 1, 2, 4, and 8.5 hr following the last dose on day 1. Additional blood samples were collected before the 1st, 2nd, 3rd, 4th dose and at 0.5, 1, 2, 4, 8, and 12 hours after the last dose on day 90. Gatifloxacin concentrations in plasma were measured using a validated LC-MS/MS method with LOQ

The results are summarized in the table below. Following repeat topical ocular administrations of 0.5% gatifloxacin ophthalmic solution to dogs, gatifloxacin was absorbed into systemic circulation. There was no big difference between male and female dogs. No accumulation was noted.

Plasma TK data of gatifloxacin in dogs (Mean ± SD)

	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)
1-month	Day 7			Day 28		
Male	59.3± 22.6	4.50± 0.84	472± 161	63.2± 25.1	4.50± 0.84	554± 219
Female	88.2± 39.7	4.58± 0.20	690± 201	66.9± 18.7	5.00± 0.45	679± 128
Overall	73.7± 34.3	4.54± 0.58	581± 208	65.0± 21.2	4.75± 0.69	616± 183
	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)
3-month	Day 1			Day 90		
Male	145± 68	11.3± 6.0	1830± 390	17.2± 4.0	5.92± 1.93	168± 42
Female	179± 174	17.0± 1.3	2140± 1200	18.9± 3.9	5.25± 2.27	196± 51
Overall	162± 127	14.2± 5.1	1980± 870	18.0± 3.9	5.58± 2.04	182± 47

Pharmacokinetic Studies on Gatifloxacin Ophthalmic Solution Distribution and Metabolism in Rabbits (Report no. 5990902) Vol. 11, Page 320.

Key study findings:

Following a single topical ocular administration of 0.5% gatifloxacin to rabbits, radioactivity was rapidly absorbed into the eye without being metabolized. It, as other fluoroquinolones, bound to melanin pigmented tissues.

Study Nº: -2652
Report Nº: 5990902
Vol/Page: Vol.11, Page 320
Conducting laboratory/location: [redacted]

Date of study initiation: July 24, 1998
GLP: Not indicated.
QA report: Yes ( ) No (X)
Drug: Gatifloxacin (Lot#: G685311a)
^{14}C-gatifloxacin (Lot#: CFQ10804, 2.16 MBq/mg)
Methods: Liquid scintillation counting
Dosing: Single bilateral dose, 25 µl/drop x 2 in a 5 min interval
Species/strain: Male Dutch belted rabbits, 1.71-2.08 kg,
Male JW rabbits, 1.86-2.16 kg
N: 4/group.
Age: Age data were not provided.
The purpose of this study was to determine the ocular concentrations of gatifloxacin following a topical ocular administration of ^{14}C-gatifloxacin solution 0.5% (200 kBq/rabbit) to male Dutch and Japanese white (JW) rabbits. Animals were treated topically with a single bilateral dose (50 µl/eye, 25 µl/drop x 2 in a 5 min interval) of ^{14}C-gatifloxacin 0.5% ophthalmic solution. Plasma and ocular tissues (aqueous humor, cornea, iris-ciliary body, conjunctiva, extraocular muscle, sclera, lens, vitreous body, retina, and choroid tissues) were collected at 0.5, 1, 2, 4, 8, 24 hr and 7, 28, and 84 days post-dose from Dutch rabbits and at 1, 4, and 24 hr post-dose from Japanese white rabbits. A total of four rabbits were sampled at each time point. The radioactivity concentration in tissues was determined by liquid scintillation counting. For metabolite profiling, the supernatants of selected tissue homogenates from Dutch rabbits were analyzed by TLC.

Results:

The results are summarized in the table below. In both strains, radioactivity was distributed to the ocular tissues rapidly with high concentrations of radioactivity noted in cornea and conjunctival tissues. The radioactivity in iris-ciliary body and choroid tissues of the pigmented strain was much higher than that in the non-pigmented strain, suggesting that gatifloxacin might have a high affinity for melanin. Melanin binding is a known characteristic of quinolones.

Comparison of tissue distribution between pigmented and non-pigmented rabbits

	Dutch belted rabbits			Japanese white rabbits		
Tissue	Tmax (hr)	Cmax(ng-eq/ml)	T1/2	Tmax (hr)	Cmax(ng-eq/ml)	T1/2
Plasma	0.5	63	(Tmax-2hr) 0.81 hr	1	16	
Cornea	0.5	8951	(Tmax-24hr) 4.6 hr (7-84 day) 22 days	1	3269	(Tmax-24hr) 2.8 hr
Conjunctiva	0.5	1768	(Tmax-24hr) 5.6 hr (7-84 day) 31 days	1	1077	(Tmax-24hr) 2.8 hr
Extraocular muscle	0.5	530	(Tmax-24hr) 5.3 hr	1	158	(Tmax-24hr) 4.7 hr
Sclera	0.5	719	(Tmax-8hr) 3.6 hr (24hr-84day) 23 days	1	319	(Tmax-24hr) 24.3hr
Iris-ciliary body	8	7562	Not calculated (Tmax-84day) 22 days	1	435	(Tmax-24hr) 5.8 hr
Aqueous humor	1	987	(Tmax-24hr) 4.1 hr	1	480	(Tmax-24hr) 3.2 hr
Lens	1	22	(Tmax-24hr) 1.0 day	1	18	(Tmax-24hr) 1.9 days
Vitreous body	1	20	(Tmax-24hr) 12 hr	1	9	(Tmax-24hr) 3.6 days
Retina	0.5	125	(Tmax-8hr) 9.4 hr (24hr-84day) 38 days	24	97	Not calculated
choroid	24	2264	Not calculated (Tmax-84day) 41 days	1	191	(Tmax-24hr) 1.4 days

() = time points used in t ½ calculation.

In the metabolism assay, the results showed that ^{14}C-gatifloxacin was a major component and the relative amounts of metabolites were slight in these tissues, suggesting that gatifloxacin is distributed to the ocular tissues without being metabolized.

Pharmacokinetic Studies on Gatifloxacin Ophthalmic Solution at Three Concentrations in Rabbits (Report no. 5990904) Vol. 11, Page 400.

Key study findings:

Following a single ocular dose of ^{14}C-gatifloxacin into the eyes of rabbits, radioactivity was rapidly distributed to cornea, conjunctiva and aqueous humor with a Tmax value of 0.25 to 0.5 hr. The highest radioactivity concentrations in these tissues were reached in rabbits treated at 0.3% gatifloxacin. Radioactivity concentrations were not increased at 0.5% gatifloxacin.

Study N^{o}: [redacted]-2809, D99-C01
Report N^{o}: 5990904
Vol/Page: Vol.11, Page 400
Conducting laboratory/location: [redacted]

Date of study initiation: July 1, 1999
GLP: Not indicated
QA report: Yes ( ) No (X)
Drug: Gatifloxacin (Lot#: G685311)
^{14}C-gatifloxacin (Lot#: CFQ10804, 2.16 MBq/mg)
Methods: [redacted]
Dosing: Single unilateral dose, 25 µl/drop x 2 in a 5 min interval
Species/strain: Male JW rabbits
N: 4/group.
Age/weight: Age data were not provided. Weight: 1.81-2.23 kg
The purpose of this study was to determine the pharmacokinetics of gatifloxacin in ocular tissues following a single topical ocular administration to Japanese white rabbits. Animals were treated topically with a single dose of ^{14}C-gatifloxacin 0.1% (113 kBq/0.05 mg), 0.3% (50 kBq/0.15 mg), and 0.5% (50

kBq/0.25 mg) ophthalmic solution (given unilaterally as two 25 µl instillations within 5-min). Aqueous humor, conjunctiva, and cornea were collected at 0.25, 0.5, 1, and 2 hours post-dose. The total radioactivity concentration in each of these tissues was determined by liquid scintillation counting.

Results:

The results are summarized in the table below. At all three dose levels, the highest radioactivity concentration was in cornea, followed by conjunctiva and aqueous humor. Gatifloxacin distributed rapidly to these tissues and reached peak concentrations in all tissues between 0.25 and 0.5 hr after dosing, except in aqueous humor of the 0.3% group, which peaked at 1 hr. Increasing the dose from 0.1% to 0.3% resulted in 2-6 times higher tissue radioactivity, reflecting a dose response. Increasing the dose from 0.3% to 0.5% did not show a dose-response, an indication of saturation of exposure. However, the sponsor indicated that this was possibly due to differences in pH between the formulations (0.3% formulation pH = 6.0; 0.5% formulation pH = 5.5).

Radioactivity Concentrations in Ocular Tissues Following a Single Ophthalmic Administration of [^{14}C]-Gatifloxacin at Three Concentrations to Albino Rabbits

Group	Tissue	Radioactivity Concentration (ng-eq/g or mL)			
		0.25 hr	0.5 hr	1 hr	2 hr
0.1 % (0.05 mg)	Conjunctiva	1010 ± 646	578 ± 447	280 ± 198	140 ± 80
	Cornea	3813 ± 860	3613 ± 2354	1707 ± 337	1250 ± 185
	Aq. Humor	195 ± 20	281 ± 175	206 ± 39	142 ± 19
0.3 % (0.15 mg)	Conjunctiva	4810 ± 5783	1265 ± 241	906 ± 486	265 ± 139
	Cornea	21460 ± 13491	7719 ± 2130	6751 ± 3723	4520 ± 465
	Aq. Humor	850 ± 551	829 ± 170	1120 ± 546	881 ± 139
0.5 % (0.25 mg)	Conjunctiva	1721 ± 1220	1738 ± 1451	598 ± 473	186 ± 194
	Cornea	9350 ± 1488	12229 ± 7056	4820 ± 1728	2273 ± 792
	Aq. Humor	590 ± 79	1192 ± 852	882 ± 495	419 ± 111

Mean ± SD of 4 rabbits

Pharmacokinetic Studies on Gatifloxacin Ophthalmic Solution with and without Preservative in Rabbits (Report no. 9936) Vol. 12, Page 001.

Key study findings:

Following a single topical ocular administration of ^{14}C-gatifloxacin 0.3% ophthalmic solutions with and without preservative to rabbits, there was no marked difference in the radioactivity concentrations in ocular tissues between the solutions.

Study Nº: [redacted]-2610
Report Nº: 9936
Vol/Page: Vol.12, Page 001
Conducting laboratory/location: [redacted]

Date of study initiation: July 01, 1999
GLP: Not indicated.
QA report: Yes ( ) No (X)
Drug: Gatifloxacin (Lot#: G685311)
^{14}C-gatifloxacin (Lot#: CFQ10804, 2.16 MBq/mg)
Methods: [redacted]

QA report: Yes ( ) No (X)
Drug: Gatifloxacin (Lot#: G725341)
^{14}C-gatifloxacin (Lot#: CFQ12144, 1.66 MBq/mg)
Methods: Liquid scintillation counting
Dosing: Single bilateral dose, 25 µl/drop x 2 in a 5 min interval
Species/strain: Male Dutch rabbits, 1.69-2.22 kg
N: 3/group.
Age/weight: Age data were not provided.
The purpose of this study was to determine the distribution and elimination of gatifloxacin following a single topical ocular administration of ^{14}C-gatifloxacin 0.3% to Dutch rabbits. Animals were treated topically with a single dose of ^{14}C-gatifloxacin 0.3% (534 kBq/0.3 mg/animal) ophthalmic solution (given bilaterally as two 25 µl instillations within 5-min). Three rabbits were sampled at each time point. Blood and ocular tissues (right eyes: aqueous humor, cornea, iris-ciliary body, conjunctiva, extraocular muscle, sclera, lens, vitreous body, retina, and choroid tissues) were collected at 0.5, 1, 2, 4, 8, and 24 hr and 7, 28, and 84 days post-dose. Systemic tissue samples (cerebrum, cerebellum, heart, lung, liver, kidney, skin, stomach, small and large intestines, stomach content, and intestine content) were collected from the animals that were terminated at 0.5, 1, and 24 hr and 7 and 28 days after dosing. Urine and feces were collected from 3 animals during a period between 24 and 168 hr after dosing. Eyeball samples were collected from one animal each at 1 and 24 hr and 7 days after instillation for [redacted]
The total radioactivity concentration in tissues was determined by liquid scintillation counting.

Results:

Ocular and systemic distribution: The results are summarized in the tables below. Radioactivity in ocular tissues reached peak concentrations in most tissues by 2 hrs post-dose. The highest radioactivity concentrations were detected in cornea and iris-ciliary body. Radioactivity slowly disappeared from the iris-ciliary body and retina/choroid most likely because of binding to melanin.

Radioactivity Concentrations in Selected Tissues after a Single Dose of ^{14}C-Gatifloxacin to the Eyes of Dutch Rabbits

	Gatifloxacin Concentration (ng-eq/ mL)								
Tissue	0.5 hr	1 hr	2 hr	4 hr	8 hr	24 hr	7 day	28 day	84 day
Plasma	29 ± 9	43 ± 7	15 ± 4	5 ± 2	3 ± 3	0 ± 0	0 ± 0	1 ± 2	0 ± 0
Aqueous humor	615 ± 141	506 ± 155	377 ± 61	104 ± 23	25 ± 10	3 ± 2	1 ± 1	0 ± 0	0 ± 0
Conjunctiva	295 ± 174	170 ± 52	250 ± 257	33 ± 20	77 *	17 ± 8	48 ± 74	0 ± 0	0 ± 0
Cornea	6178 ± 540	3948 ± 1227	2183 ± 202	903 ± 179	276 ± 156	48 ± 13	42 ± 51	2 ± 3	0 ± 0
ICB	1458 ± 105	2036 ± 205	4247 ± 1219	4706 ± 1097	6492 ± 3955	3172 ± 1096	1765 ± 468	936 ± 317	181 ± 42
Lens	13 ± 6	23 ± 6	23 ± 4	13 ± 8	13 ± 8	5 ± 3	0 ± 1	0 ± 1	0 ± 0
Vitreous body	4 ± 1	5 ± 0	4 ± 0	3 ± 1	2 ± 2	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Retina & choroid	487 ± 316	551 ± 73	841 ± 394	800 ± 71	636 ± 146	474 ± 149	376 ± 45	298 ± 64	130 ± 76
Sclera	493 ± 197	484 ± 71	328 ± 90	390 ± 91	228 ± 162	103 ± 20	75 ± 36	36 ± 20	9 ± 2
Heart	61 ± 21	81 ± 12		10 ± 3		0 ± 0	0 ± 0	0 ± 0	
Lung	69 ± 21	86 ± 10		11 ± 4		3 ± 0	0 ± 0	0 ± 0	
Liver	234 ± 71	349 ± 58		37 ± 12		4 ± 2	0 ± 0	0 ± 0	
Kidney	260 ± 94	276 ± 12		49 ± 9		4 ± 1	0 ± 0	0 ± 0	
Skin	18 ± 7	38 ± 7		5 ± 1		1 ± 1	0 ± 0	0 ± 0	
Stomach	150 ± 129	122 ± 23		30 ± 18		2 ± 2	0 ± 0	0 ± 0	
Small intestine	467 ± 96	829 ± 555		21 ± 7		3 ± 1	0 ± 0	0 ± 0	

Data are expressed as the mean values ± S.D. of three animals.

PK parameters of radioactivity in ocular tissues

Tissues	T1/2 (day)	$AUC_{0\text{-}84day}$ (μg-eq hr/ml)	$AUC_{0\text{-}\infty}$ (μg-eq hr/ml)
Cornea	3.2	32.7	33.0
Iris-ciliary body	21	1900	2030
Retina and choroid	38	533	705

Elimination: The drug excretion into urine and feces is summarized in the table below. The major route of excretion was through feces. Following a single ocular dose of ^{14}C-gatifloxacin to Dutch rabbits, the majority of the administered dose was excreted within 24 hours and excretion was almost complete by 48 hours.

Cumulative Excretion of Radioactivity in Urine and Feces after a Single Dose of [14C]-Gatifloxacin to the Eyes of Male Dutch Rabbits

	Excretion of radioactivity (% of dose)		
Time (hr)	Urine	Feces	Total
0 - 24	30.8 ± 8.3	54.7 ± 9.9	85.5 ± 1.6
48	33.8 ± 8.8	60.9 ± 11.5	94.7 ± 2.7
72	34.6 ± 8.9	61.8 ± 11.3	96.4 ± 2.4
96	34.7 ± 9.0	62.2 ± 11.3	96.9 ± 2.4
120	35.0 ± 9.0	62.3 ± 11.2	97.2 ± 2.3
144	35.1 ± 9.1	62.3 ± 11.2	97.3 ± 2.2
168	35.1 ± 9.1	62.3 ± 11.2	97.3 ± 2.2
Cage washing (168 hr)			0.0 ± 0.0

Data are expressed as the mean values ± S.D. of three animals

the 43rd instillation, ocular tissues, blood, and selected body tissues were collected (n=3/timepoint) for radioactivity measurements. The total radioactivity concentration in tissues was determined by liquid scintillation counting.

Results:

The results are summarized in the table below. In most ocular tissues, the radioactivity concentrations at one hour after the 10th, 22nd and 43rd instillation did not increase with the continuous treatment. The radioactivity levels in lens and sclera were 2.5 times and 1.7 times higher after the 10th instillation, respectively and 3.1 times and 3.2 times higher after the 22nd instillation, respectively in comparison with the levels after the initial instillation. However, the levels after the 43rd instillation were similar to those observed after the 22nd instillation, indicating that steady-state was achieved. The radioactivity in iris-ciliary body and choroid/retina, in comparison with that after the initial instillation, respectively increased to 13 and 8.5 times after the 10th instillation, 16 and 13 times after the 22nd instillation, and 20 and 24 times after the 43rd instillation. Steady-state was not observed in iris-ciliary body and choroid/retina after the 43rd instillation.

Radioactivity Concentrations in Selected Tissues after a Single and Repeated Doses of [^{14}C]-Gatifloxacin to the Eyes of Dutch Rabbits

	Radioactivity concentration (ng-eq/g or mL)			
Tissue	**Single dose***	**10 doses**	**22 doses**	**43 doses**
Plasma	43 ± 7	30 ± 4	26 ± 3	29 ± 4
Blood	40 ± 7	29 ± 4	27 ± 4	29 ± 3
Aqueous humor	506 ± 155	579 ± 263	516 ± 81	552 ± 2
Conjunctiva	170 ± 52	227 ± 90	209 ± 68	227 ± 30
Extraocular muscle	97 ± 15	65 ± 10	56 ± 9	74 ± 7
Cornea	3948 ± 1227	4290 ± 1315	4322 ± 1387	3658 ± 152
ICB	2036 ± 205	26425 ± 5811	31657 ± 7439	40286 ± 4254
Lens	23 ± 6	58 ± 12	72 ± 2	74 ± 6
Vitreous body	5 ± 0	7 ± 1	6 ± 5	9 ± 2
Retina & choroid	551 ± 73	4682 ± 1305	7321 ± 2329	13144 ± 1232
Sclera	484 ± 71	820 ± 80	1540 ± 136	1815 ± 567
Lacrimal gland	129 ± 32	82 ± 13	85 ± 8	91 ± 15
Sub lacrimal gland	49 ± 4	37 ± 8	34 ± 13	35 ± 5
Nasal mucus mem	67 ± 17	54 ± 12	59 ± 4	63 ± 3
Tongue	581 ± 322	231 ± 70	314 ± 89	391 ± 80
Liver	349 ± 58	235 ± 14	216 ± 12	239 ± 15
Skin	38 ± 7	32 ± 5	37 ± 4	42 ± 8

Data are expressed as the mean values ± S.D. of three animals. (0.15 mg/eye, 0.3 mg/body TID)

The elimination of radioactivity from iris-ciliary body and choroid/retina after the 43rd instillation was slower in comparison with that from the remaining tissues (see table below). The slow elimination from sclera was considered attributable to the insufficient removal of melanin tissue of choroid attached to the sclera.

Radioactivity concentrations in tissues after 2-week (43 times) topical administration of ^{14}C-gatifloxacin in Dutch rabbits (ng-eq/g or ml, mean ± SD)

Tissue	1 hr	4 hr	8 hr	7 days	84 days	T1/2 (day)	$AUC_{0-\infty}$(mg-eq hr/ml
Plasma	29± 4	7± 6	0	0	0		
Aqueous humor	552± 2	138± 36	64± 18	12± 6	0		
Conjunctiva	227± 30	157± 49	72± 57	45± 25	0		
Extraocular muscle	74± 7	24± 4	9± 3	4± 8	0		
Cornea	3658± 152	1097± 142	394± 71	102± 25	0	5.3	88.0
Iris-ciliary body	40286± 4254	40628± 9810	37417± 6251	17571± 2534	1308± 269	17	14700
Lens	74± 6	64± 16	58± 13	13± 5	0		
Vitreous body	9± 2	8± 2	5± 1	0	0		
Retina/choroid	13144± 1232	11754± 3350	9525± 2360	8734± 2955	1178± 670	24	7170
Sclera	1815± 567	1297± 115	1098± 280	885± 293	90± 42	21	721
Lacrimal gland	91± 15	28± 2	10± 10	0	0		
Nasal mucous membrane	63± 3	13± 12	0	0	0		
Tongue	391± 80	54± 19	28± 7	0	0		
Liver	239± 15	102± 4	47± 20	5± 4	0		
Skin	42± 8	16± 0	3± 5	3± 3	0		

The above results indicated that when ^{14}C-gatifloxacin was repeatedly instilled into the eyes of Dutch rabbits, the radioactivity concentrations in tissues containing melanin increased with the instillation frequency. However, despite the slower disappearance of radioactivity in these tissues after the 43rd instillation in comparison with other tissues, steady elimination of ^{14}C-gatifloxacin was observed, suggesting that the binding to melanin was reversible.

Melanin Affinity of BMS-206584 (AM-1155): In Vitro Binding Assay (BMS Study no. 910059199) Vol. 12, Page 257.

This is an abstract.
The purpose of this study was to determine the *in vitro* affinity of gatifloxacin and other fluroquinolones [fleroxacin (FLRX), pefloxacin (PFLX), norfloxacin (NFLX), ciprofloxacin (CPFX), ofloxacin (OFLX), and lomefloxacin (LFLX)] for acid-insoluble melanin from bovine eyes.. Chloroquine and befunolol were used as positive control. Binding was measured by adding one ml of each compound solution (ranging from 0.2-4000 µg/ml) to 1 ml of melanin suspension (0.2 mg/ml). The mixture was incubated for 24 hr at 25 °C. The binding was determined by the liquid scintillation spectrometry and HPLC. The results showed that all of the agents exhibited saturable melanin binding with increasing concentration. At 1 µg/ml and 10 µg/ml, gatifloxacin was 66.9% and 36.9% melain-bound, respectively. At 1 µg/ml, the order of binding to melanin was as fellows: chloroquine > befunolol > CPFX ≥ NFLX > PFLX > OFLX > LFLX > gatifloxacin > FLRX; and at 10 µg/ml, chloroquine > befunolol > CPFX > PFLX ≥ NFLX > OFLX > gatifloxacin ≥ LFLX > FLRX.

PK/TK summary and conclusions:

Following single or repeated topical ocular administrations to rabbits and dogs, gatifloxacin was absorbed systemically. The drug was also rapidly absorbed into the rabbit eye without being metabolized. High concentrations were noted in the tissues containing melanin (iris-ciliary body, retina-choroid) and in cornea with long half-life values. The highest radioactivity concentrations in these tissues were reached at 0.3% gatifloxacin. The drug bound to melanin pigmented tissues as other fluoroquinolones. The majority of the administered dose was excreted within 24 hours and the excretion was almost complete (94.7%) by 48 hours. The fecal excretion was the major elimination pathway for gatifloxacin.

METHODS

Test Article: 0.5% gatifloxacin ophthalmic solution

Formulation of 0.5% gatifloxacin ophthalmic solution (%, w/v)

Gatifloxacin hydrate	[redacted]
NaCl	[redacted]
HCl	[redacted]
NaOH	
Distilled water	qs

Batch No: Lot No. 8P28
Purity: Not stated
Vehicle Control: Physiologic saline
Species/Strain: Japanese White rabbits, 11 weeks old, 1.98-2.13 kg
No. of Animals: 3 males
Route: Topical ophthalmic into the right eye of each animal; the left eye was dosed similarly with the control material.
Dose Volume (µl): 100
Concentration: 0.5%
Treatment Schedule: 8 times per day at approximate hourly intervals for 7 days

Observations:
Clinical signs: Daily
Body weights: Prior to dosing and at the end of the week
Ocular examination including fluorescein staining: Following the last dosing on the 1st, 4th, and 7th day of study)

RESULTS

Clinical Signs: No remarkable observations were noted.
Body Weights: No remarkable observations were noted.
Ophthalmology: No remarkable observations were noted.

In conclusion, 0.5% gatifloxacin was not irritating to the rabbit eye following 8 instillations per day for 7 days.

Four-Week Repeated Dose Ocular Instillation Toxicity Study of Gatifloxacin in Rabbits

Key study findings: Gatifloxacin ophthalmic solution at concentrations of 1.0% and 0.5% were not irritating to the rabbit eye or systemically toxic following 4 instillations in each eye per day for 4 weeks.

Report No. 9937
Study Code: H-98182
Vol/Page: Vol. 12, Page 275
Study Dates: May 29 – October 30, 1998
Report Date: October 30, 1998
Study Purpose: To assess the potential toxicity of gatifloxacin to the rabbit eye.
Test Facility: [redacted]

GLP Status: Compliant with Japanese GLP MHW Ordinance No. 21, 1997

METHODS

Test Article: Gatifloxacin hydrate and 0.5% gatifloxacin ophthalmic solution
Batch No: Gatifloxacin hydrate – G725341 (The drug was [redacted]
Gatifloxacin ophthalmic solution (0.5%) - Lot no. 8P28 (The sponsor indicated that this solution was formulated. No detailed formulation information was provided.)
Purity: Gatifloxacin hydrate - [redacted]
Gatifloxacin ophthalmic solution (0.5%) – [redacted]
Vehicle Control: Physiologic saline
Species/Strain: Dutch rabbits, 21 weeks old, 1.73-1.97 kg
No. of Animals: 5 males/group
Route: Topical ophthalmic application into both eyes.
Dose Volume (µl): 100
Concentration: 0, 0.5, and 1.0%
Treatment Schedule: Four times per day at approximately 2.5-hour intervals for 4 weeks.

Observations:
Clinical signs – Twice daily
Body weights – Weekly
Ophthalmology
Anterior portion including slit lamp – Weekly
Cornea with fluorescein and slit lamp – Weekly
Optic media – Weekly
Ocular fundus – Weekly
Electroretinogram – Day 0 and Weeks 1 and 4
Urinalysis – Week 4
Hematology – Week 4
Blood chemistry – Week 4
Necropsy – Week 4
Organ weights – Week 4; Eyeballs with Harderian glands, brain, pituitary, submandibular glands, thymus, heart, lungs, liver, kidneys, spleen, adrenal glands, thyroids and testes
Histopathology – Week 4 (bulbur conjunctiva, palperbral conjunctiva, optic nerve, lacrimal glands and Harderian glands, gross lesions)

RESULTS

Clinical Signs: No treatment-related observations were noted.
Body Weights: No treatment-related observations were noted.
Ophthalmology: No treatment-related observations were noted.
Urinalysis: No treatment-related observations were noted.
Hematology: No treatment-related observations were noted.
Blood chemistry: No treatment-related observations were noted.
Necropsy: No treatment-related observations were noted.
Organ weights: No treatment-related observations were noted. A slight decrease in heart weight was noted in the animals at 1.0% gatifloxacin group (see table below). Histopathological examination showed no corresponding lesions. Therefore, the decrease in the heart weight was not considered treatment-related.

Heart weight changes in rabbits (mean ± SD)

Treatment	[redacted]	0.5% gatifloxacin	1.0 gatifloxacin
Heart weight (g)	4.84± 0.19	4.53± 0.16	4.32± 0.22

Relative weight (g/kg)	2.66± 0.12	2.44± 0.16	2.40± 0.17

Histopathology: No treatment-related observations were noted.

In conclusion, 1.0% and 0.5% gatifloxacin ophthalmic solution were not irritating to the rabbit eye or systemically toxic following 4 instillations in each eye per day for 4 weeks.

28-Day Repeat Dose Ocular Instillation Toxicity Study with 0.5% Gatifloxacin Ophthalmic Solution in Rabbits

Key study findings: Gatifloxacin, 0.5%, in 0.005% benzalkonium chloride and — disodium edetate preservative was not irritating to the rabbit eye or systemically toxic following 8 instillations in each eye per day for 4 weeks.

Report N^{o}: 9932
Study Code: 7029-100
Vol/Page: Vol.13, Page 001
Study Purpose: To assess the toxicity of 0.5% gatifloxacin ophthalmic solution when administered by ocular instillation into both eyes of rabbits 8 times per day for 30 days
Study Dates: April 7 – August 30, 1999
Report Date: August 30, 1999
Test Facility: —
GLP Status: Compliant with FDA GLP 21 CFR 58

METHODS

Test Article: 0.5% gatifloxacin with 0.005% banzalkonium chloride and — disodium edetate as preservative (The formulation is similar to the clinical formulation.)
Batch No: Lot No. 9M09
Purity: —
Vehicle Control: 0.9% sodium chloride for injection
Species/Strain: Haz:(NZW)SPF albino rabbits, 13 weeks old, 2.11-2.53 kg
No. of Animals: 5 males/group
Route: Topical ophthalmic into both eyes
Dose Volume (µl): 100
Concentration: 0.5%
Treatment Schedule: Eight times per day at approximately 2-hour intervals for 30 days

Observations:
Clinical signs – Twice daily
Body weight – Weekly
Ophthalmology
Gross observation for ocular irritation - Once daily (prior to the 1st dosing)
Indirect ophthalmoscopy and slit lamp biomicroscopy – Weekly
Intraocular pressure – Weekly
Fluorescein angiography – Weekly
Electroretinogram – Prior to initiation and days 14 and 30
Hematology – Prior to treatment and at termination
Blood chemistry – Prior to treatment and at termination
Necropsy – Week 4
Organ weights – Week 4 (adrenal, brain, heart, kidney, liver, lung, pituitary, prostate, spleen, and testis)

Histopathology – Week 4 (eye, conjunctiva, optic nerve, Harderian gland, lacrimal gland, and gross lesions; remaining tissues were preserved for possible future examination)

RESULTS

Clinical signs: No treatment-related observations were noted.
Body weight: No treatment-related observations were noted.
Ophthalmology: No treatment-related observations were noted.
Hematology: No treatment-related observations were noted.
Blood chemistry: No treatment-related observations were noted.
Necropsy: No treatment-related observations were noted.
Organ weights: No treatment-related observations were noted.
Histopathology: No treatment-related observations were noted.

In conclusion, 0.5% gatifloxacin in 0.005% benzalkonium chloride and [redacted] disodium edetate preservative was not irritating to the rabbit eye or systemically toxic following 8 instillations in each eye per day for 4 weeks. The drug was well tolerated.

Gatifloxacin (AGN 198172): A 1- and 3-Month Ocular Toxicity Study in Dogs

Key study finding: Gatifloxacin ophthalmic solution 0.5% exhibited a very low ocular irritation potential evidenced by the reversible and mild conjunctival hyperemia. No toxicologically significant ocular or systemic toxicity was elicited.

Study Nº: TX00065
Protocol Nº: 2000-3032
Vol/Page: Vol.13, Page 268
Report Date: October 27, 2001
Compound: 0.5% gatifloxacin ophthalmic solution (Lot #: 00599C. Purity = [redacted] . Formulations were **similar** to the clinical formulation.)
Route: Ocular, topical [2 drops (80 µl), right eye only]
Animal: Beagle dogs, 13-14 months old, 7.5-11.1 kg for females and 7.5-11.4 kg for males, 6/sex/group
Study Initiation: January 16, 2001
Study Facility: [redacted]

GLP/QAU: Yes
Study Design:

Group	Treatment	Dosing frequency	Duration	N/sex (Total)	N/sex (Recovery)
1	Vehicle	10/day [2 drops(80 µl) every 30 min]	30 days	6	2
2	Vehicle	32/day [2 drops(80 µl) every 30 min] x 2 days, 16/day x5 days, then qid thereafter	90 days	6	2
3	0.5% gatifloxacin	10/day [2 drops(80 µl) every 30 min]	30 days	6	2
4	0.5% gatifloxacin	32/day [2 drops(80 µl) every 30 min] x2 days, 16/day x5 days, then qid thereafter	90 days	6	2

The purpose of this study was to determine the ocular toxicity of gatifloxacin ophthalmic solution following daily ocular instillations to beagle dogs for 1 or 3 consecutive months followed by a 1-month recovery period. The day of the first dosing was designated as day 1. Toxicity was assessed as shown below.

Mortality:	Twice daily
Clinical signs:	Once daily
Body weights:	Once weekly
Food consumption:	Daily
Ophthalmoscopy:	
--Gross ocular observation:	During treatment period: Twice daily during the 1st week and twice weekly thereafter During recovery period: Once weekly
--Ophthalmology:	Ophthalmological examination, including slit lamp biomicroscopy with fluorescein staining, indirect ophthalmoscopy, pupillary reflex, and IOP, were conducted prior to the treatment, at the ends of the treatment and recovery periods.
Hematology:	Weeks 4 and 13
Clinical chemistry:	Weeks 4 and 13
Urinalysis:	Weeks 4 and 13
Gross pathology:	All animals
Organs weighed:	The following organs from all animals were weighed: adrenals, brain, heart, kidneys, liver, pituitary, ovaries, testes, and thymus.
Histopathology:	Histopathological examination was performed on the tissues listed in the Histopathology Inventory Table from all groups.
Toxicokinetics:	TK assay was reviewed in the PK/TK section.

Results:

Clinical observations: No mortality and drug-related abnormal findings were noted.

Body weight: No treatment-related differences in body weights were noted between control and treated animals.

Food consumption: The repeated treatment with gatifloxacin showed no adverse effect on mean food consumption. Group 4 males showed higher food consumption relative to the Group 2 controls (163-360 g/day for Group 2 males vs. 221-400 g/day for Group 4 males). However, the increased food consumption was noted in both pretreatment period (128-311 g/day for Group 2 males vs. 163-363 g/day for Group 4 males) and treatment period (163-360 g/day for Group 2 males vs. 221-400 g/day for Group 4 males), and was not accompanied by differential body weight gain. Similar changes were not seen in female animals. Hence, it was not considered as treatment-related.

Gross ocular observations: In male animals, mild conjunctival hyperemia (score =1) was noted in both eyes in both control and treated animals (see table below). The incidence and frequency of mild hyperemia in treated eyes (right eyes) appeared higher than in untreated eyes (left eyes), mostly among animals receiving the more intensive treatment (Groups 2 and 4). The incidence and frequency of mild hyperemia in the drug-treated eyes appeared higher than in the vehicle-treated eyes. Hyperemia was rarely noted among the females. There was no drug-related hyperemia during the recovery phases.

Total incidence of positive gross ocular observation findings (total # of incidence-days/animal involved)

Group	1	3	2	4	1recovery	3recovery	2recovery	4recovery
	Vehicle	Treatment	Vehicle	Treatment	Vehicle	Treatment	Vehicle	Treatment
Males								
N	6	6	6	6	2	2	2	2
Hyperemia								
Treated eye		8/3	10/2	30/6				2/2
Untreated eye		2/1		2/1				
Both eyes		6/1	3/2	7/2		2/1		1/1
Chemosis								
Treated eye		4/1				2/1		1/1
Untreated eye								
Both eyes		2/1						
Discharge								
Treated eye		1/1						
Females								
N	6	6	6	6	2	2	2	2
Hyperemia								
Treated eye		3/1	1/1	1/1				
Untreated eye								
Both eyes				1/1				

Biomicroscopic evaluations: No drug-related effects were noted.

Indirect ophthalmoscopic examinations: No treatment-related changes were observed.

IOP: No toxicologically significant changes in IOP were seen.

Pupillary light reflex: No drug-related effects were noted.

Clinical pathology: No toxicologically significant, biologically relevant findings in hematology, coagulation, clinical chemistry and urinalysis were observed.

Gross necropsy: No abnormalities or gross lesions were noted.

Organ weights: No drug-related differences in either absolute or relative organ weights were observed between control and treated animals. Group 2 females showed a higher ovary weight relative to the other groups (2.1 g vs. 1.4 g, 1.5 g and 1.1 g in the Groups 1, 3 and 4, respectively). Similar findings were not observed in the recovery animals. Histopathological examination showed no correlated findings.

Histopathology: No treatment-related abnormal findings were present in ocular and nonocular tissues.

TK assay: TK data are summarized in the table below. Gatifloxacin was systemically absorbed following ocular dosing. Plasma Cmax and AUC values were comparable on day 7 and day 28.

TK data in animals treated with 0.5% gatifloxacin ophthalmic solution (mean ± SD)

Group	Day	Cmax (ng/ml)	Tmax (hr)	$AUC_{0-\infty}$ (ng-hr/ml)
3	7	73.7± 34.3	4.54± 0.58	581± 208
	28	65.0± 21.2	4.75± 0.69	616± 183
4	1	162± 127	14.2± 5.1	1980± 870
	90	18.0± 3.9	5.58± 2.04	182± 47

In summary, beagle dogs were treated topically with 0.5% gatifloxacin ophthalmic solutions for up to 3 months (10 times daily for 1 month or 32 times per day for 2 days, 16 times per day for 5 days and 4

times daily for the rest of the 3 months). No adverse drug-related changes in clinical signs, body weight, food consumption and clinical pathology were observed. Drug-related effects were limited to mild but reversible conjunctival hyperemia mainly observed in male animals. Slit-lamp biomicroscopy, indirect ophthalmoscopy of the fundus, IOP measurements, pupillary light reflex measurements revealed no findings attributable to topical ocular treatment with gatifloxacin ophthalmic solution. Post-mortem examinations showed no treatment-related abnormal findings. In conclusion, 0.5% gatifloxacin ophthalmic solution was well tolerated with a very low ocular irritation potential. No significant ocular and systemic toxicity following 3-month topical ocular administration was observed.

Histopathology Inventory for NDA 21-493

Study	TX00065
Species	dogs
Adrenals	+
Aorta	+
Bone Marrow smear	+
Bone (femur, tibia, 12th rib)	+
Brain	+
Cecum	+
Cervix	
Colon	+
Duodenum	+
Epididymis	+
Esophagus	+
Eye with eyelids, lacrimal glands and ocular muscles	+
Femoral cartilage	+
Gall bladder	+
Gross lesions	+
Harderian gland	
Heart	+
Ileum	+
Injection site	
Jejunum	+
Kidneys	+
Lachrymal gland	
Larynx	
Liver	+
Lungs	+
Lymph nodes, cervical	
Lymph nodes mandibular	+
Lymph nodes, mesenteric	+
Mammary Gland	+
Nasal cavity	
Optic nerves	+
Ovaries	+
Pancreas	+
Parathyroid	+
Peripheral nerve	
Pharynx	
Pituitary	+
Prostate	+
Rectum	+
Salivary gland	+
Sciatic nerve	+
Seminal vesicles	
Skeletal muscle	+
Skin	+
Spinal cord	+

Spleen	+
Sternum	+
Stomach	+
Testes	+
Thymus	+
Thyroid	+
Tongue	
Trachea	+
Urinary bladder	+
Uterus	+
Vagina	+
Urethra	+
Ureters	+

Summary and conclusion:

Four ocular toxicity studies with duration up to 3 months were conducted in rabbits or dogs. The results indicated that gatifloxacin ophthalmic solution with the concentrations up to 0.5% exhibited a very low ocular irritation potential. No significant ocular and toxicity was elicited.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Gatifloxacin by oral and iv routes has been approved for more than two years and has been considered as safe, effective and well-tolerated. Nonclinical PK studies with gatifloxacin ophthalmic solution showed that the drug was rapidly absorbed and well distributed in the eye following topical ocular administration. Ocular toxicity studies in rabbits and dogs with the duration up to 3 months showed the drug was safe with a very low ocular irritation potential. In summary, nonclinical studies submitted in this NDA support the safety of the drug product.

General Toxicology Issues:

No toxicologically significant issues were indicated.

Recommendations:

This application is approvable from a nonclinical perspective with some minor modifications of labeling as revised in the "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy" and "Animal and in vitro Pharmacology" sections.

Labeling with basis for findings:

Original version:

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

X. APPENDIX/ATTACHMENTS:

Addendum to review: No

Other relevant materials (Studies not reviewed, appended consults, etc.): No

Any compliance issues: No

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zhou Chen
1/22/03 04:16:20 PM
PHARMACOLOGIST

Josie, Please sign this NDA review. I have made all corrections based on your version. Thanks, Zhou

Josie Yang
1/22/03 04:47:18 PM
PHARMACOLOGIST