

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**21-061 and 21-062**

**PHARMACOLOGY/TOXICOLOGY REVIEW**

**Review and Evaluation of Pharmacology and Toxicology Data  
Division of Anti-Infective Drug Products, HFD-520**

**NDA #s:** 21,061-000 (Oral); 21,062-000 (IV)

**Date CDER Received:** 12/28/98

**Reviewer:** Amy L. Ellis, Ph.D.

**Date Assigned:** 1/5/99

**Number of Volumes:** 296 total (51 for pharm/tox)

**Date Review Started:** 1/14/99

**Date 1<sup>ST</sup> Draft Completed:** 11/1/99

**KEY WORDS:** Tequin, gatifloxacin, fluoroquinolone, oral, intravenous, phototoxicity, pancreas

**Sponsor:** Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, CT 06492  
Phone: (203) 677-6883; Fax: (203) 677-7630

**Authorized Representative:** Douglas Kriesel, Ph.D.  
Director, Worldwide Regulatory Affairs

**Manufacturer:** Kyorin Pharmaceutical Company, Ltd.  
Okaya Plant  
Nagano, Japan

**Review Contains Information to be Communicated to Sponsor:** Yes

**Submission Contains Any Integrated Tox Study Summaries in Lieu of Final Reports:** No

**Drug Information:**

**Class:** Fluoroquinolone antimicrobial, DNA gyrase inhibitor

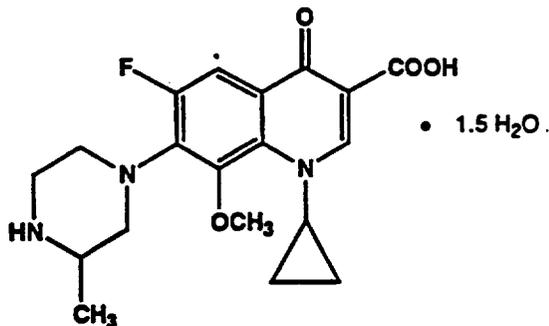
**Code Names:** BMS-206584; AM-1155; CG-5501

**Generic Name:** Gatifloxacin

**Trade Name:** Tequin

**Chemical Name:** 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

**Structure:**



**Relevant INDs/NDA's/DMFs:**

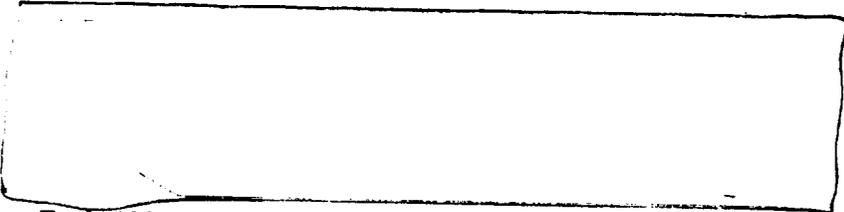
**Indications:** Community acquired pneumonia, acute exacerbation of chronic bronchitis, acute sinusitis, complicated and uncomplicated urinary tract infections, uncomplicated skin and skin structure infections, gonococcal infections. The daily recommended dose of gatifloxacin will be 400 mg/day for 7-14 days for most of these indications. The exceptions are uncomplicated UTI and gonococcal infections where the recommended doses will be 200 mg/day for 3 days or a single dose of 400 mg.

**Clinical Formulations/Routes of Administration:**

Each 200 mg Tequin Oral Tablet contains:

Gatifloxacin	200 mg
Microcrystalline Cellulose	<span style="border: 1px solid black; display: inline-block; width: 80px; height: 15px;"></span>
Sodium Starch Glycolate	<span style="border: 1px solid black; display: inline-block; width: 80px; height: 15px;"></span>
Magnesium Stearate	<span style="border: 1px solid black; display: inline-block; width: 80px; height: 15px;"></span>
Total Tablet Weight	306 mg

\*Composition of Coating Suspension (per 200 mg tablet):



Each 400 mg Oral Tablet contains twice as much of each ingredient as the 200 mg tablets contain.

Tequin I.V. will be packaged in single use vials containing 200 mg (20 ml) or 400 mg (40 ml) of gatifloxacin in a sterile, preservative-free solution. The contents of the vials are intended to be diluted to 2 mg/ml in an appropriate infusion solution prior to use. Each ml of this solution for intravenous use contains:

Gatifloxacin	
Dextrose (anhydrous)	
HCl and/or NaOH	
Water for Injection	

Tequin I.V. will also be available in a ready to use, preservative-free formulation of 2 mg/ml gatifloxacin in 5% dextrose. This solution will be packaged in flexible infusion bags in a 100 ml or 200 ml volume.

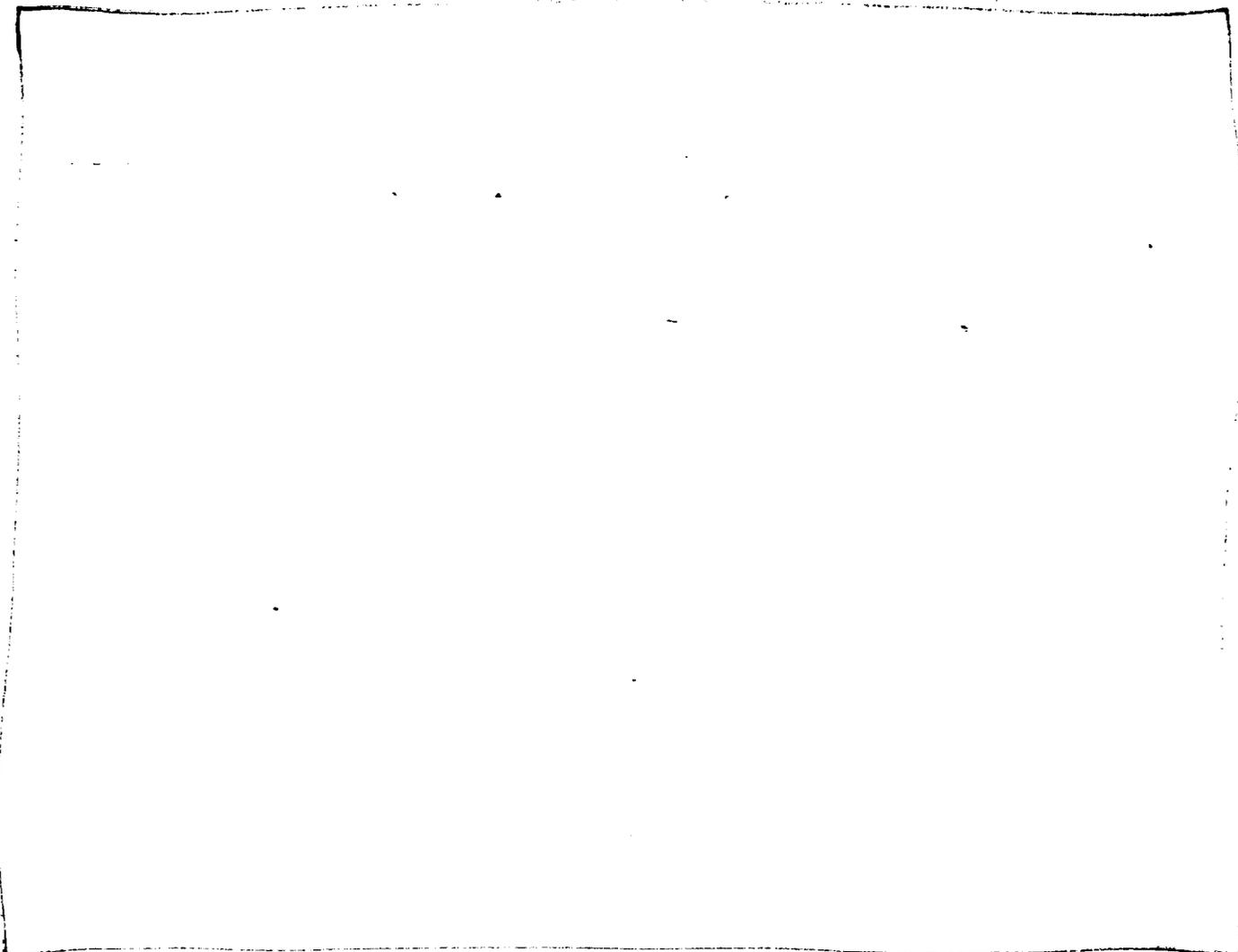
**Introduction and Drug History:** Gatifloxacin is a member of the fluoroquinolone antimicrobial group and is an inhibitor of bacterial DNA gyrase. Like some of the other newer quinolones, it can be administered once daily and has a broader spectrum of antimicrobial activity than many of the older drugs in this class (active against gram positive organisms as well as gram negative). The sponsor has submitted data suggesting that gatifloxacin has a much lower phototoxic potential than some of the other quinolones. Many of the nonclinical toxicity studies conducted with gatifloxacin have been performed by Kyorin Pharmaceutical Company in Japan. Bristol-Myers Squibb obtained the right to develop and market gatifloxacin from Kyorin.

**Studies reviewed within this submission:**

**Nonclinical Metabolism and Pharmacokinetics:**

\*Contains data from a toxicokinetic study conducted to support a nonclinical toxicology study

Synthesis of [2'-<sup>14</sup>C]-Gatifloxacin (BMS-206584 ) (BMS Report No. 910062410)



**Pharmacokinetics and Dose Proportionality of Gatifloxacin (BMS-206584, [redacted]) in Dogs (BMS Report No. 910062406)**

**\*Measurement of Serum Gatifloxacin Concentrations During a "One Month Oral Range-Finding Study of Gatifloxacin in Monkeys (SBL 11-50)" (BMS Report No. 910070347)**

**\*Measurement of Serum Gatifloxacin Concentrations During a "Five Month Oral Toxicity Study of Gatifloxacin in Monkeys (SBL 11-51)" (BMS Report No. 910070348)**

**One-Week Oral Toxicokinetics Study in Rats, Study No. A97ER09 (BMS Report No. 910070398)**

**Toxicokinetic Report for Study No. A97ED07: One-Week Oral Toxicokinetic Study of Gatifloxacin in Dogs (BMS Report No. 910072454)**

**Toxicokinetics of Gatifloxacin (BMS-206584, [redacted]) During a 13-Week Dietary Preliminary Carcinogenicity Study of Gatifloxacin in Mice, Study No. K94GM02 (BMS Report No. 910062407)**

**One-Month Dietary Toxicokinetics Study in Mice, Study No. KS97137 (BMS Report No. 910070390)**

**BMS-206584: One-Month Dietary Toxicokinetics Study in Rats, Kyorin Study No. A97ER08 (BMS Report No. 910072261)**

**Absorption of Gatifloxacin from Gastrointestinal Segments in the Rat (BMS Report No. 910070170)**

**Autoradiography, Site of Absorption, and Biliary Excretion Study of <sup>14</sup>C-Gatifloxacin After Single Oral Administration in Rats (BMS Report No. 910072414)**

**Structural Elucidation and Quantification of Metabolites of Gatifloxacin in Rats, Rabbits, and Dogs (BMS Report No. 910070349)**

**Absorption, Distribution, and Excretion of <sup>14</sup>C-Gatifloxacin After Repeated Intravenous Administration in Rats (BMS Report No. 910068389)**

**\*Toxicokinetics of Gatifloxacin in Kyorin Study No. C92ED07: Oral Study of Articular Toxicity in Immature Dogs (BMS Report No. 910058205)**

**Gatifloxacin: Maternal-Fetal Transfer and Excretion in Breast Milk in Rats (BMS Report No. 910072415)**

**BMS-206584: Oral Toxicokinetics Study in Pregnant Rabbits, Kyorin Study No. A98EU07 (BMS Report No. 910072260)**

**Intraocular Pharmacokinetics of Gatifloxacin in Pigmented Rats (BMS Study No. 910070168)**

**Mass Balance, Absorption, and Disposition Study of [<sup>14</sup>C]Gatifloxacin (BMS-206584) in Male Dogs, Study No. 744/206584/001 (BMS Report No. 910070237)**

**Toxicology:**

**Repeat Dose Studies:**

**BMS-206584: Two-Week Dietary Range-Finding Study in Mice, Study No. 2201 (167-001) (BMS Report No. 910070405)**

**BMS-206584: Three-Month Dietary Range-Finding Study in Mice (I), Study No. 2223 (167-002) (BMS Report No. 910070406)**

**BMS-206584: Three-Month Dietary Range-Finding Study in Mice (II), Study No. K92GM02 (BMS Report No. 910070279)**

**BMS-206584: Two-Week Dietary Range-Finding Study in Rats, Study No. K92GR01 (BMS Report No. 910070389)**

**BMS-206584: Three-Month Dietary Range-Finding Study in Rats, Study No. K92GR03 (BMS Report No. 910070278)**

**Reproduction and Developmental Toxicity Studies:**

**BMS-206584: Preliminary Oral Study of Fertility and Early Embryonic Development in Rats, Study No. C90FRA6 (BMS Report No. 910070421)**

**BMS-206584: Preliminary Oral Study of Embryo-Fetal Development in Rats, Study No. C91TRA2 (BMS Report No. 910070419)**

**BMS-206584: Preliminary Intravenous Study of Embryo-Fetal Development in Rats, Study No. C92TRA1 (BMS Report No. 910070420)**

**BMS-206584: Preliminary Oral Study of Embryo-Fetal Development in Rabbits, Study No. C91TUA4 (BMS Report No. 910070418)**

**Genetic Toxicology Studies:**

**BMS-206584: Oral DNA Repair Study in Rats (I), Study No. C931106 (BMS Report No. 910062571)**

**BMS-206584: Oral DNA Repair Study in Rats (II), Study No. 18250-0-494 (BMS Report No. 910060757)**

**Special Toxicity Studies:**

**BMS-206584: Single-Dose Intravenous Phototoxicity Study in Mice, Study No. C91EM13 (BMS Report No. 910070391)**

**BMS-206584: Single-Dose Oral Phototoxicity Study in Guinea Pigs, Study No. A95VG05 (BMS Report No. 910070392)**

**BMS-206584: Photosensitivity Potential in Guinea Pigs (BMS Report No. 910062570)**

**BMS-206584: Photosensitization Study in Guinea Pigs (I), Study No. C94EG17 (BMS Report No. 910072025)**

**BMS-206584: Photosensitization Study in Guinea Pigs (II), Study No. C95EG01 (BMS Report No. 910072024)**

**BMS-206584: Effects of Intravenous Infusion on Pulmonary Function in Anesthetized Guinea Pigs, Study No. OF-PH 346 (BMS Report No. 910070393)**

**BMS-206584: Local Tolerability After Single Intravenous, Intraarterial, and Paravenous Injection in the Rabbit, Study No. FO-TP2004/96 (BMS Report No. 910062572)**

**Toxicity Studies with Impurities of BMS-206584:**

**BMS-206584 Impurities: Single-Dose Oral Toxicity Study in Rats (I), Study No. A96AR16 (BMS Report No. 910070394)**

**BMS-206584 Impurities: Single-Dose Oral Toxicity Study in Rats (II), Study No. A96AR25 (BMS Report No. 910070397)**

**BMS-206584 Impurities: Two-Week Oral Toxicity Study in Rats, Study No. A97SR03 (BMS Report No. 910070422)**

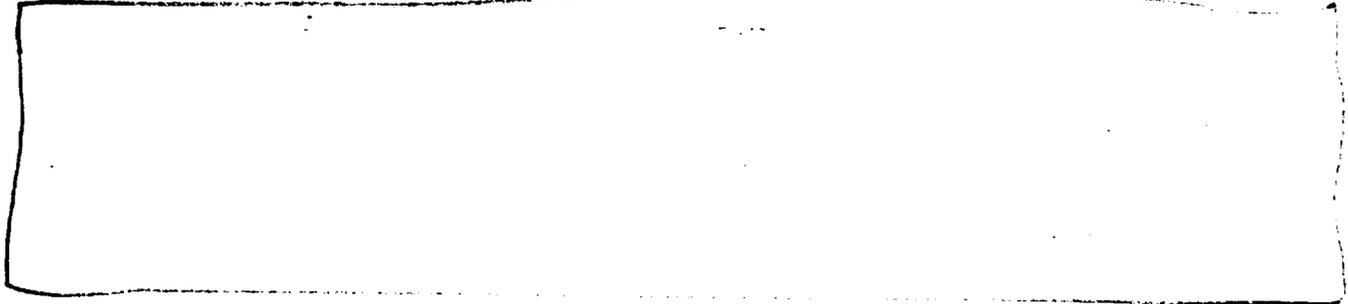
**BMS-206584 Impurities: Ames Reverse-Mutation Study in Salmonella and Escherichia coli, Study No. A96MB10 (BMS Report No. 910070395)**

**BMS-206584 Impurities: Cytogenetics Study in Chinese Hamster Lung Cells, Study No. A96MC11 (BMS Report No. 910070396)**

Studies not reviewed within this submission (and location of review):

Nonclinical Metabolism and Pharmacokinetics:

\*Contains data from a toxicokinetic study conducted to support a nonclinical toxicology study



Pharmacokinetic Study of BMS-206584 [redacted] in Mice and Rats (BMS Report No. 910059197); [redacted]

Presence or Absence of Chiral Inversion of BMS-206584 [redacted] in the Rat, Dog, and Monkey (BMS Report No. 910059204); [redacted]

Pharmacokinetics of BMS-206584 [redacted] New Quinolone, and Its Optical Isomers in Mice, Rats, Rabbits, Dogs, and Monkeys (BMS Report No. 910059196); [redacted]

\*Measurement of Serum BMS-206584 [redacted] Concentrations During a "Six-Month Oral Repeated Dose Toxicity Study of [redacted] in Rats (K91CR03)" (BMS Report No. 910059195); [redacted]

Toxicokinetics of BMS-206584 [redacted] During a 2-Week Dietary Range-Finding Study of BMS-206584 in Rats, Study No. T-9202 (BMS Report No. 910058590); [redacted]

Toxicokinetics of BMS-206584 [redacted] During a 3-Month Dietary Preliminary Carcinogenicity Study of BMS-206584 in Rats, Study No. T-9208 (BMS Report No. 910058591); [redacted]

\*Toxicokinetics of BMS-206584 [redacted] During a 2-Year Carcinogenicity Study of BMS-206584 in Rats, Study No. T-9305 (BMS Report No. 910058592) Included in a separate review of carcinogenicity studies filed under NDA 21,061

Absorption, Distribution, and Excretion of <sup>14</sup>C-BMS-206584 (<sup>14</sup>C [redacted]) After Single Intravenous Administration in Rats (BMS Report No. 910059201); [redacted]

Absorption, Distribution, and Excretion of <sup>14</sup>C-BMS-206584 (<sup>14</sup>C [redacted]) After Single Oral Administration in Rats (BMS Report No. 910059200); [redacted]

**Absorption, Distribution, and Excretion of  $^{14}\text{C}$ -BMS-206584 ( $^{14}\text{C}$  [redacted] After Repeated Oral Administration in Rats (BMS Report No. 910059206); [redacted]**

**Drug Interaction of BMS-206584 ([redacted] and Theophylline in Rats (BMS Report No. 910072413 contains same data as 910059203); [redacted]**

**Intraocular Pharmacokinetics of BMS-206584 ([redacted] in Pigmented Rabbits (BMS Report No. 910059202); [redacted]**

**\*Measurement of Serum BMS-206584 ([redacted] Concentrations During a "Six-Month Oral Repeated Dose Toxicity Study [redacted] in Dogs (K91CD06)" (BMS Report No. 910059205); [redacted]**

**Distribution of BMS-206584 ([redacted] into Cerebrospinal Fluid and Brain Tissue in Dogs (BMS Report No. 910059198); [redacted]**

**Melanin Affinity of BMS-206584 ([redacted] In Vitro Binding Assay (BMS Report No. 910059199); [redacted]**

**Toxicology:**

**Single Dose Studies:**

**BMS 206584: Single-Dose Oral Toxicity Study in Rats, Study No. K90AR03 (BMS Report No. 910058088); [redacted]**

**BMS 206584: Single-Dose Oral Toxicity Study in Dogs, Study No. K90AD06 (BMS Report No. 910058087); [redacted]**

**BMS 206584: Single-Dose Intravenous Toxicity Study in Rats, Study No. K90AR04 (BMS Report No. 910058093); [redacted]**

**BMS 206584: Single-Dose Intravenous Toxicity Study in Dogs, Study No. K90AD07 (BMS Report No. 910058086); [redacted]**

**Repeat Dose Studies:**

**BMS 206584: One-Month Oral Toxicity Study in Rats, Study No. C90SR06 (BMS Report No. 910058080); [redacted]**

**BMS 206584: One-Month Oral Toxicity Study in Dogs, Study No. C90SD15 (BMS Report No. 910058079); [redacted]**

**BMS 206584: One-Month Oral Range-Finding Study in Monkeys, Study No. SBL 11-50**  
(BMS Report No. 910058094) [Reviewed by Terry S. Peters, DVM, filed separately under [REDACTED]]

**BMS 206584: Five-Month Oral Toxicity Study in Monkeys, Study No. SBL 11-51** (BMS Report No. 910058089) [Reviewed by Terry S. Peters, DVM, filed separately under [REDACTED]]

**BMS 206584: Five-Month Oral Toxicity Study in Monkeys- Ultrastructural Evaluation, Study No. C93ES06** (BMS Report No. 910058518) [Reviewed by Terry S. Peters, DVM, filed separately under [REDACTED]]

**BMS 206584: Six-Month Oral Toxicity Study in Rats, Study No. K91CR03** (BMS Report No. 910058078) [Reviewed by Terry S. Peters, DVM, filed separately under [REDACTED]]

**BMS 206584: Six-Month Oral Toxicity Study in Dogs, Study No. K91CD06** (BMS Report No. 910058085) [Reviewed by Terry S. Peters, DVM, filed separately under [REDACTED]]

**BMS 206584: Six-Month Oral Toxicity Study in Dogs- Ultrastructural Evaluation, Study No. C92ED08** (BMS Report No. 910058090) [Reviewed by Terry S. Peters, DVM, filed separately under [REDACTED]]

**BMS 206584: One-Month Intravenous Toxicity Study in Rats, Study No. KS90085** (BMS Report No. 910058216); [REDACTED]

**BMS 206584: One-Month Intravenous Toxicity Study in Dogs, Study No. KS91025** (BMS Report No. 910058083); [REDACTED]

**Reproduction and Developmental Toxicity Studies:**

**BMS 206584: Oral Study of Fertility and Embryonic Development in Rats, Study No. C90FR17** (BMS Report No. 910058091); [REDACTED]

**BMS 206584: Oral Study of Embryo-Fetal Development in Rats, Study No. C91TR04** (BMS Report No. 910058077); [REDACTED]

**BMS 206584: Oral Study of Embryo-Fetal Development in Rabbits, Study No. C92TU01** (BMS Report No. 910058081); [REDACTED]

**BMS 206584: Intravenous Study of Embryo-Fetal Development in Rats, Study No. C92TR05** (BMS Report No. 910058092); [REDACTED]

**BMS 206584: Oral Study of Pre- and Postnatal Development in Rats, Study No. KS95060** (BMS Report No. 910058220); [REDACTED]

**Genetic Toxicology Studies:**

**BMS-206584: Ames Reverse-Mutation Study in Salmonella and Escherichia Coli, Study No. C91MB03 (BMS Report No. 910058219);** [redacted]

**BMS-206584: V-79 Mammalian-Cell Forward Gene-Mutation Study (I), Study No. C92MC19 (BMS Report No. 910058212);** [redacted]

**BMS-206584: V-79 Mammalian-Cell Forward Gene-Mutation Study (II), Study No. C93MC07 (BMS Report No. 910058211);** [redacted]

**BMS-206584: Cytogenetics Study in Chinese Hamster Lung Cells (I), Study No. C90MC05 (BMS Report No. 910058218);** [redacted]

**BMS-206584: Cytogenetics Study in Chinese Hamster Lung Cells (II), Study No. C93MC01 (BMS Report No. 910058217);** [redacted]

**BMS-206584: Oral Micronucleus Study in Mice, Study No. C90MM19 (BMS Report No. 910058213);** [redacted]

**BMS-206584: Intravenous Micronucleus Study in Mice, Study No. C90MM18 (BMS Report No. 910058214);** [redacted]

**BMS-206584: Oral Cytogenetics Study in Rats, Study No. C90MR21 (BMS Report No. 910058215);** [redacted]

**BMS-206584: Genotoxicity Studies (BMS Report No. 910058302);** [redacted]

**Carcinogenicity Studies:**

**BMS-206584: Dietary Carcinogenicity Study in Mice, Study No. KS95012 (BMS Report No. 910065003); reviewed under NDA 21,061-000, but filed separately**

**BMS-206584: Dietary Carcinogenicity Study in Rats, Study No. C92GR20 (BMS Report No. 910058202) [Reviewed by Terry S. Peters, DVM, filed separately under** [redacted]

**Special Toxicity Studies:**

**BMS-206584: Safety Pharmacology (BMS Report No. 910058084);** [redacted]

**BMS-206584: Interaction Study with Fenbufen (BMS Report No. 910058095);** [redacted]

**BMS-206584: Safety Evaluation of Racemic BMS-206584 and Its Optical Isomers** (BMS Report No. 910058100); [REDACTED]

**BMS-206584: Antigenicity Study in Mice, Study No. K91IM05** (BMS Report No. 910058203); [REDACTED]

**BMS-206584: Antigenicity Study in Guinea Pigs, Study No. C90IG10** (BMS Report No. 910058204); [REDACTED]

**BMS-206584: Phototoxicity Study in Mice, Study No. C92EM03** (BMS Report No. 910058206); [REDACTED]

**BMS-206584: Comparative Phototoxicity Study in Guinea Pigs** (BMS Report No. 910058209); [REDACTED]

**BMS-206584: Oral Study of Articular Toxicity in Juvenile Rats** (BMS Report No. 910058208); [REDACTED]

**BMS-206584: Oral Study of Articular Toxicity in Immature Dogs, Study No. C92ED07** (BMS Report No. 910058205); [REDACTED]

**BMS-206584: Osteotoxicity Study in Rats and Dogs** (BMS Report No. 910058301); [REDACTED]

**BMS-206584: Intramuscular Irritation Study in Rabbits, Study No. C91LU05** (BMS Report No. 910058210)

**BMS-206584: Intravenous Irritation Study in Rabbits, Study No. 93384** (BMS Report No. 910058207); [REDACTED]

**BMS-206584: Intravenous Nephrotoxicity Study in Rabbits, Study No. C92EU04** (BMS Report No. 910058099); [REDACTED]

**BMS-206584: Oral Study of Ophthalmotoxicity in Pigmented Rabbits** (BMS Report No. 910058201); [REDACTED]

**BMS-206584: Effect on Histamine Release in Dogs** (BMS Report No. 910058098); [REDACTED]

**BMS-206584: Effects on Pancreatic Beta Cells** (BMS Report No. 910058300); [REDACTED]

**REVIEWS OF PRECLINICAL PHARMACOLOGY AND TOXICOLOGY STUDIES:**

**Nonclinical Metabolism and Pharmacokinetics:**

\*Contains data from a toxicokinetic study conducted to support a nonclinical toxicology study

Synthesis of [2'-<sup>14</sup>C]-Gatifloxacin (BMS-206584 [redacted] BMS Report No. 910062410)

Y. Asahina (Kyorin Pharmaceutical Co., Japan)

Report dated: 5/17/95

Vol. 50, pp. 120-130

**Summary:** This is a description of the synthesis method for <sup>14</sup>C-labeled gatifloxacin, including purification and determination of radiochemical purity and specific activity.

[redacted]

Report dated: 7/31/98

Vol. 51, 32-67

**Summary:** A [redacted]

[redacted]

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

**Pharmacokinetics and Dose Proportionality of Gatifloxacin (BMS-206584, [REDACTED])  
[REDACTED] in Dogs (BMS Report No. 910062406)**

H. Kusajima, T. Ooie, R. Ishida, H. Uchida (Kyorin Pharmaceutical Co., Japan)

Report dated: 11/18/96

Vol. 53, pp. 60-76

**Summary:** Groups of 5 male beagle dogs received 2, 15, or 30 mg/kg single oral doses of gatifloxacin. The same animals received the 15 and 30 mg/kg doses with a 6 day washout period between. Blood samples were drawn from the dogs that received the 2 mg/kg dose 0.25, 0.5, 1, 2, 3, 5, 7, 9, 12, and 24 hours after dosing. Blood samples were drawn from the dogs that received 15 or 30 mg/kg gatifloxacin 0.5, 1, 2, 4, 6, 9, 12, and 24 hours after dosing. Serum gatifloxacin concentrations were measured [REDACTED]

The pharmacokinetic parameters of gatifloxacin in these dogs were as follows:

**Mean (+SD) Pharmacokinetic Parameters of Gatifloxacin  
in Beagle Dogs After Oral Administration**

	<b>2 mg/kg</b>	<b>15 mg/kg</b>	<b>30 mg/kg</b>
<b>T<sub>max</sub> (hr)</b>	1.1 ± 0.5	1.7 ± 0.7	1.8 ± 0.4
<b>C<sub>max</sub> (µg/ml)</b>	0.91 ± 0.06	7.65 ± 1.44	13.0 ± 1.3
<b>AUC<sub>0-∞</sub> (µg·hr/ml)</b>	7.17 ± 0.8	71.1 ± 11.9	138 ± 24
<b>T<sub>1/2</sub> (hr)</b>	5.8 ± 0.7	6.1 ± 1.0	7.0 ± 1.8

The C<sub>max</sub> and AUC rose in a dose proportional manner between 2 and 30 mg/kg. T<sub>max</sub> was slightly longer after the 15 and 30 mg/kg doses than after the 2 mg/kg dose and T<sub>1/2</sub> was slightly longer after the 30 mg/kg dose than the 2 lower doses, but the relatively small differences may be due solely to variability.

**\*Measurement of Serum Gatifloxacin Concentrations During a "One Month Oral Range-Finding Study of Gatifloxacin in Monkeys (SBL 11-50)" (BMS Report No. 910070347)**

H. Kusajima, C. Komiya, R. Ishida, H. Ohkubo (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 7/23/98

Vol. 53, pp. 77-92

**Summary:** Blood samples were drawn from cynomolgus monkeys (2/sex) during an ascending dose study where the animals received doses of 10, 20, 60, and 100 mg/kg/day. Each dose level was used for one week of the study. Blood was drawn from the animals 2 and 24 hours after the first dose (10 mg/kg) and the last dose on day 28 of the study (100 mg/kg). Serum concentrations of gatifloxacin were measured [redacted]

Serum concentrations were similar for male and females receiving the same dose of gatifloxacin. There appeared to be a potential for accumulation at the high dose.

**Gatifloxacin Concentrations in Serum from Cynomolgus Monkeys**

Dose	Animal ID		Gatifloxacin Concentrations (µg/ml)	
			2 hr	24 hr
10 mg/kg	Male	1		
		2		
	Female	1		
		2		
100 mg/kg	Male	1		
		2		
	Female	1		
		2		

**\*Measurement of Serum Gatifloxacin Concentrations During a "Five Month Oral Toxicity Study of Gatifloxacin in Monkeys (SBL 11-51)" (BMS Report No. 910070348)**

H. Kusajima, R. Ishida, H. Ohkubo (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 7/23/98

Vol. 53, pp. 93-109

**Summary:** Blood samples were drawn from male and female cynomolgus monkeys 2 hours after dosing during weeks 13 and 20 of a 5 month study where the animals received doses of 15 (n=3/sex), 30 (n=3/sex), and 60 (n=5/sex) mg/kg/day. Serum concentrations of gatifloxacin were measured [redacted]

**Gatifloxacin Concentrations in Serum from Cynomolgus Monkeys  
2 hours After Dosing (average ± SD, µg/ml)**

	15 mg/kg	30 mg/kg	60 mg/kg
<b>Week 13</b>			
<b>Males</b>	[redacted]		
<b>Females</b>			
<b>Week 20</b>			
<b>Males</b>			
<b>Females</b>			

There appeared to be no gender differences in gatifloxacin exposure in the monkeys. Serum levels rose in a roughly dose-proportional manner. There did not appear to be any drug accumulation between weeks 13 and 20 of the study at these dose levels.

**One-Week Oral Toxicokinetics Study in Rats, Study No. A97ER09 (BMS Report No. 910070398)**

In life phase: Y. Kasahara (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 7/29/98 (Kyorin); 7/9/98 (BMS)

Vol. 53, pp. 135-276

**Summary:** Male and female Wistar rats (6 weeks old, 24/sex/group, food and water *ad libitum*) were given daily oral doses of 30, 60, 120, 240, or 810 mg/kg gatifloxacin (suspended in 0.3% carboxymethyl cellulose) for one week. Blood samples were drawn from 3 rats/sex/time point 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing on days 1 and 7 as well as prior to dosing on day 7. The concentration of gatifloxacin was measured in plasma [redacted]

The study was conducted to determine exposure parameters following the doses used in the 4 week and 26 week oral rat studies.

**Mean Toxicokinetic Parameters of Gatifloxacin  
in Rats Given Oral Drug Daily for 7 Days**

Dose (mg/kg)	Day	Cmax (µg/ml)		AUC <sub>0-24</sub> (µg·hr/ml)	
		Females	Males	Females	Males
30	1	0.88	0.98	2.83	3.78
	7	1.43	1.09	3.82	4.20
60	1	2.20	1.98	7.40	8.16
	7	2.71	2.42	8.43	9.92
120	1	5.54	5.09	17.83	23.77
	7	5.52	4.26	20.02	23.94
240	1	8.62	7.79	35.20	41.88
	7	8.03	8.34	41.23	45.71
810	1	16.19	16.36	129.15	162.51
	7	19.55	23.27	154.16	261.45

Tmax ranged from 0.5-2 hours during the study, but was usually 0.5-1 hr. There did not appear to be a gender difference in toxicokinetics. Plasma concentration and AUC rose in a roughly dose proportional manner. For most doses, there appeared to be no accumulation over the course of the study, but at 810 mg/kg there may have been a small amount of accumulation.

**Toxicokinetic Report for Study No. A97ED07: One-Week Oral Toxicokinetic Study of Gatifloxacin in Dogs (BMS Report No. 910072454)**

In life phase: S. Takano, Y. Kaneko, K. Takizawa, Y. Sato (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 8/28/98 (Kyorin); 7/27/98 (BMS)

Vol. 53, pp. 277-362

**Summary:** Male and female beagle dogs (11-12 months old, 3/sex/group, 300 g food/day and water *ad libitum*) were given daily oral doses of 6, 12, or 24 mg/kg gatifloxacin (in gelatin capsules) for one week. The same animals were used throughout the study with a 14 day washout period between dose levels and male/female pairs received the doses in different orders. Blood samples were drawn 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing on days 1 and 7 as well as prior to dosing on day 7. Occasional vomiting was observed during the study at all dose levels. The concentration of gatifloxacin was measured in plasma. The study was conducted to determine exposure parameters following the doses used in the 26 week oral dog study.

**Mean Toxicokinetic Parameters of Gatifloxacin  
in Dogs Given Oral Drug Daily for 7 Days**

Dose (mg/kg)	Day	C <sub>max</sub> (µg/ml)		AUC <sub>0-24</sub> (µg·hr/ml)	
		Females	Males	Females	Males
6	1	2.1	1.6	14.5	15.3
	7	2.0	1.7	15.3	14.3
12	1	2.8	2.8	27.3	25.4
	7	3.2	3.1	31.2	28.4
24	1	6.5	5.5	64.2	59.4
	7	5.8	4.7	66.5	46.9

T<sub>max</sub> ranged from 1-4 hours during the study, but was usually around 2 hr. There did not appear to be a gender difference in toxicokinetics. Plasma concentration and AUC rose in a roughly dose proportional manner. There appeared to be no accumulation over the course of the study.

**Toxicokinetics of Gatifloxacin (BMS-206584 [redacted]) During a 13-Week Dietary Preliminary Carcinogenicity Study of Gatifloxacin in Mice, Study No. K94GM02 (BMS Report No. 910062407)**

Y. Mitsuoka, T. Tachiiri, K. Momo, H. Kusajima (Kyorin Pharmaceutical Co., Tokyo, Japan)

Report dated: 10/16/96

Vol. 54, pp. 1-19

**Summary:** This is the toxicokinetics portion of a pilot study to assist in dose setting for a mouse carcinogenicity study with dietary administration. Mice were fed a dietary admixture containing 0.05%, 0.12% or 0.3% gatifloxacin and blood samples were drawn from 3 male and 3 female animals per dose group on one day during week 2 of dosing 9 AM, 1 PM, 5 PM, 9 PM, 1 AM, 5 AM, and 9 AM (the next morning). During week 12, blood samples were similarly drawn at 9 AM and 5 PM on one day. [redacted] was used to determine the concentration of gatifloxacin in the serum. The serum concentrations and AUC of gatifloxacin increased in a dose dependant manner and were similar between males and females. The concentrations did not differ much between weeks 2 and 12 of dosing. The 24 hour AUCs during week 2 for males and females at 0.05%, 0.12%, and 0.3%, were 6.2, 13.6, 37.5, and 8.3, 16.9, 43.2 µg·hr/ml, respectively.

**One-Month Dietary Toxicokinetics Study in Mice, Study No. KS97137 (BMS Report No. 910070390)**

[redacted]  
Report dated [redacted] 3/17/98 (BMS)

Vol. 54, pp. 78-174

**Summary:** Male and female B6C3F<sub>1</sub> mice (6 weeks old) were fed a diet containing 0.015%, 0.03%, and 0.06% gatifloxacin for one month. Blood samples were collected from 3 mice/sex at each of the following time points during a 24 hour period during the final week of dosing: 7 PM, 11 PM, 3 AM, 7 AM, 11 AM, 3 PM, and 7 PM (the following day). The concentration of gatifloxacin was measured [redacted]

**Mean Toxicokinetic Parameters of Gatifloxacin  
in Mice Given Drug in the Diet Daily for 4 Weeks**

% Drug in Diet	C <sub>max</sub> (µg/ml)		AUC <sub>0-24</sub> (µg·hr/ml)	
	Females	Males	Females	Males
0.015%	0.07	0.08	1.32	1.20
0.03%	0.17	0.13	3.28	2.20
0.06%	0.35	0.32	6.30	4.44

There did not appear to be a gender difference in toxicokinetics, as females received slightly larger doses than males on a mg/kg basis. Plasma concentration and AUC rose in a dose proportional manner.

**BMS-206584: One-Month Dietary Toxicokinetics Study in Rats, Kyorin Study No. A97ER08 (BMS Report No. 910072261)**

Y. Kuninishi, Y. Kaneko, K. Takizawa, H. Tanase, S. Takano, H. Takagi, Y. Sato (Kyorin Pharmaceutical Co., Japan)

[redacted]

Report dated: 7/14/98 (Kyorin); 6/23/98 (BMS)

Vol. 55, pp. 1-94

**Summary:** Male and female F344/Du rats (5 weeks old) were fed a diet containing 0.06%, 0.12%, and 0.24% gatifloxacin for one month. One mid dose male rat died during the study and necropsy revealed cecal torsion. Blood samples were collected from 3 rats/sex at 4 hour intervals during a 24 hour period on days 29 and 30 of dosing beginning at 7 PM. The concentration of gatifloxacin was measured [redacted] This study was conducted to supplement the rat dietary carcinogenicity study.

**Mean Toxicokinetic Parameters of Gatifloxacin  
in Rats Given Drug in the Diet Daily for 4 Weeks**

% Drug in Diet	C <sub>max</sub> (µg/ml)		AUC <sub>0-24</sub> (µg·hr/ml)	
	Females	Males	Females	Males
0.06%	0.29	0.31	4.98	5.32
0.12%	0.68	0.70	12.12	12.54
0.24%	1.44	1.46	27.90	25.46

There did not appear to be a gender difference in toxicokinetics. Plasma concentration and AUC rose in a dose proportional manner.

**Absorption of Gatifloxacin from Gastrointestinal Segments in the Rat (BMS Report No. 910070170)**

H. Kusajima, R. Ishida, H. Ohkubo (Kyorin Pharmaceutical Co., Japan)

Report dated: 6/10/98

Vol. 55, pp. 95-119

**Summary:** Fasted male Wistar rats (7-9 weeks old) were anesthetized with pentobarbital and a different segment of the GI tract (stomach, duodenum, jejunum, ileum, colon) was ligated *in situ* in each group of 4 animals. Gatifloxacin (and the other drugs tested) were dissolved in isotonic phosphate buffer (pH 6.5) at a concentration of 1.5 mM. The exception was that a pH 2 isotonic citrate buffer was used for the stomach. Each GI segment was injected with 0.2 ml of gatifloxacin solution and the segment contents were sampled 0.25, 0.5, and 1 hr after injection. Other quinolones (norfloxacin, ciprofloxacin, enoxacin, [redacted] ofloxacin and sparfloxacin) were injected into the jejunum only and sampled after one hour. At the end of the incubations, the remaining solution in the GI segments was washed out, and the tissues were sampled. Drug concentrations in sample solutions, wash solutions, and tissues [redacted]

The rates of absorption gatifloxacin over one hour were 6.9, 89.1, 92.2, 62.9, and 42.9 for the stomach, duodenum, jejunum, ileum, and colon, respectively. The amounts of drug in the tissues were relatively low, only 1.8-6.2% of the dose. In the jejunum, the absorption of gatifloxacin was better than norfloxacin, ciprofloxacin, and enoxacin, and it was approximately equal to [redacted] ofloxacin, and sparfloxacin. The absorption of gatifloxacin from the jejunum was not inhibited by amino acids (glycine and L-phenylalanine), dipeptides (glycylglycine, L-phenylalanyl-glycine) or tripeptides (glycylglycylglycine) at amino acid or peptide concentrations of 50-150 mM.

**Autoradiography, Site of Absorption, and Biliary Excretion Study of <sup>14</sup>C-Gatifloxacin After Single Oral Administration in Rats (BMS Report No. 910072414)**

N. Koseki, S. Izawa, M. Machida, A. Idesawa, R. Yuasa, M. Komuro, Y. Nagatsu, R. Ishida, H. Ohkubo, H. Uchida (Kyorin Pharmaceutical Co., Japan)

Report dated: 11/16/98

Vol. 55, pp. 120-157

**Summary:** Much of the data in this report was previously submitted in BMS Report No. 910059200. Additional findings in the current report included data from studies in male Wistar rats (6-9 weeks old) regarding biliary excretion and enterohepatic circulation of radiolabeled gatifloxacin. In bile duct cannulated rats, 26.4% of a 10 mg/kg dose of the drug was excreted into the bile within 8 hours and 97% of the total dose was recovered in bile (34.4%), urine (43.1%), and feces (20.4%). Bile collected over 4 hours from rats given 10 mg/kg of radiolabeled gatifloxacin was administered intraduodenally to other rats. About 37.1% of the radiolabel in the bile was reabsorbed after administration. As in the study directly above, various portions of the GI tract were ligated and radiolabeled gatifloxacin was administered directly to the ligated portion. Blood samples were also collected from these animals. The data from this experiment indicated that the radiolabeled drug was rapidly absorbed from the sites in the small intestine, but not the stomach. Residual radiolabel contained in the duodenum, jejunum, ileum and stomach 2 hours after administration were 20.3, 26.8, 32.4, and 81.9% of the total dose, respectively.

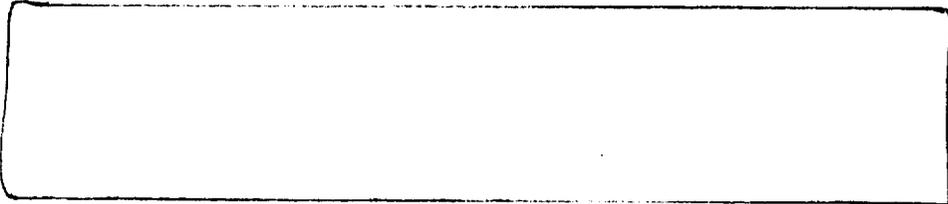
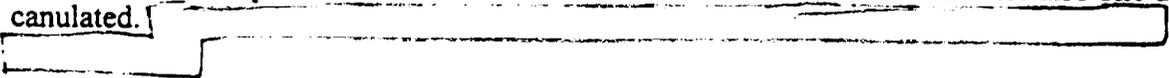
**Structural Elucidation and Quantification of Metabolites of Gatifloxacin in Rats, Rabbits, and Dogs (BMS Report No. 910070349)**

T. Ooie, H. Hashimoto, Y. Tsurumaki, M. Komuro, F. Taga, H. Ohkubo (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 7/31/98

Vol. 55, pp. 223-291

**Summary:** Oral doses of <sup>14</sup>C-gatifloxacin (10 mg/kg, 0.763-3.86 MBq) were given to groups of 3 fasted animals including male Wistar rats (8-10 weeks old), male New Zealand White rabbits (2.0-2.1 kg), and male beagle dogs (9.6-10.6 kg). Additional experiments in rats were performed with nonradiolabeled drug. Rats and rabbits received a suspension of drug in 0.3% carboxymethyl cellulose and dogs received gelatin capsules containing gatifloxacin. Animals were kept in metabolism cages for collection of urine and feces. Some rats were also bile duct cannulated.



**Recovery of Radiolabel in the Urine and Feces of Intact Rats, Rabbits  
and Dogs 24 Hours After Administration of 10 mg/kg (mean  $\pm$  SD)**

	Urine	Feces	Total
Rat	34.0 $\pm$ 11.1	66.0 $\pm$ 13.5	99.9 $\pm$ 2.5
Rabbit	33.2 $\pm$ 6.2	50.4 $\pm$ 4.3	83.6 $\pm$ 4.1
Dog	48.6 $\pm$ 5.8	21.9 $\pm$ 5.5	70.5 $\pm$ 4.6

The majority of the radiolabel in the urine of these animals (about 90%) was unchanged gatifloxacin. The percentages of the other metabolites were similar between the species, with M1 accounting for about 3% and M2, M3, and M4 accounting for about 1% each. In feces from these species, most of the radiolabel was gatifloxacin (>75%), with M2, M3, and M4 each at about 1%.

In the bile duct cannulated rats, 39.2  $\pm$  4.6% of the radiolabel dose was recovered in urine, with 43.6  $\pm$  5.2% in collected bile, and 13.2  $\pm$  2.2% in feces (total recovery of 96.1  $\pm$  1.6%). The main metabolite in bile was M1 (54% of radiolabel), followed by 18% unchanged gatifloxacin, and less than 4% M2, M3, and M4.

The metabolites M2, M3, and M4 all had 4-256 times less antibacterial activity than gatifloxacin against a panel of bacterial species.

**Absorption, Distribution, and Excretion of  $^{14}$ C-Gatifloxacin After Repeated Intravenous Administration in Rats (BMS Report No. 910068389)**

C. Toriumi, Y. Arai, n. Ishikawa, R. Ishida, H. Uchida (Kyorin Pharmaceutical Co., Japan)

Report dated: 6/10/98

Vol. 56, pp. 30-55

**Summary:** This study is a companion to a similar study where a single IV dose of the radiolabeled gatifloxacin was administered (see BMS Report No. 910059201, reviewed in ) except that this study did not include evaluation of pharmacokinetic parameters after blood sampling or bile duct cannulated rats. The methodology and lots of drug used to determine the tissue distribution of the radiolabel were the same for both studies except that the rats were not fasted in the current study and they received 7 consecutive days of IV dosing. Tissue distribution of radiolabel was similar following a single dose of  $^{14}$ C-gatifloxacin or 7 consecutive daily doses. The drug is well distributed to most tissues of the body with the exception of the CNS. Elimination of radiolabel from the bone, spleen, liver, lung, and GI tract occurred somewhat more slowly following repeated dosing than it had after the single dose. Daily urinary and fecal excretion of gatifloxacin did not change appreciably over the course of the study, suggesting a low overall potential for accumulation. However, the tissue data suggest that accumulation of small amounts of the total dose can occur in some tissues.

**\*Toxicokinetics of Gatifloxacin in Kyorin Study No. C92ED07: Oral Study of Articular Toxicity in Immature Dogs (BMS Report No. 910058205)**

H. Kusajima, Y. Sato, R. Ishida, H. Ohkubo (Kyorin Pharmaceutical Co., Japan)

Report dated: 6/10/98

Vol. 56, pp. 56-77

**Summary:** This is the toxicokinetics portion of a study conducted in immature male beagles (4 months old, 3 per dose group) to investigate articular toxicity. Gatifloxacin in gelatin capsules was given orally to the dogs daily for 7 days at doses of 5, 10, or 20 mg/kg. Blood samples were drawn on day 6 prior to dosing, then 1, 2, 4, 8, and 24 hours after dosing. On day 7, the dogs were sacrificed by exsanguination 2 hours after drug was given, and samples of blood, synovial fluid, synovial membrane, and articular cartilage were taken. [redacted] to quantitate gatifloxacin in serum and tissues from the dogs.

**Pharmacokinetic Parameters On Day 6 of Dosing (Mean ± SD)**

	5 mg/kg	10 mg/kg	20 mg/kg
C <sub>max</sub> (µg/ml)	2.35 ± 0.24	5.12 ± 0.12	7.09 ± 1.57
T <sub>max</sub> (hr)	1.7 ± 0.6	1.7 ± 0.6	3.3 ± 1.2
AUC <sub>0-∞</sub> (µg·hr/ml)	19.6 ± 2.7	41.1 ± 3.1	72.8 ± 10.0
T <sub>1/2</sub> (hr)	5.7 ± 0.5	5.35 ± 0.26	6.18 ± 1.82

C<sub>max</sub> was dose proportional between 5 and 10 mg/kg, but it was less than dose proportional between 10 and 20 mg/kg. However, AUC rose in a roughly dose proportional manner from 5-20 mg/kg. T<sub>max</sub> was greater at 20 mg/kg than at 5 or 10 mg/kg, but half life was only slightly greater (possibly due to greater variability) at 20 mg/kg.

**Serum and Joint Levels (µg/ml or µg/g, mean ± SD) of Gatifloxacin 2 hours After Dosing on Day 7**

		5 mg/kg	10 mg/kg	20 mg/kg
Serum		2.25 ± 0.14	4.68 ± 0.11	8.56 ± 0.54
Synovial Fluid	Knee	1.12 ± 0.17	3.01 ± 0.15	6.32 ± 0.95
	Hip	1.27 ± 0.10	3.14 ± 0.29	6.27 ± 0.42
	Shoulder	1.07 ± 0.23	2.96 ± 0.26	6.26 ± 0.91
Synovial Membrane	Knee	1.93 ± 0.38	4.78 ± 0.27	9.91 ± 1.81
	Hip	2.06 ± 0.47	3.88 ± 1.02	9.10 ± 2.61
	Shoulder	1.97 ± 0.28	4.28 ± 1.07	8.67 ± 3.06
Articular Cartilage	Knee	4.27 ± 0.74	8.54 ± 0.18	15.7 ± 0.8
	Hip	5.67 ± 1.17	9.54 ± 0.15	17.1 ± 3.1
	Shoulder	4.77 ± 1.01	8.75 ± 0.04	15.1 ± 1.6

The amount of gatifloxacin in joint tissues was similar between knee, hip, and shoulder joints. The concentrations in the joint tissues rose in a dose-dependant manner and were highest in articular cartilage and lowest in synovial fluid. The serum:tissue ratios for gatifloxacin in synovial fluid, synovial membrane, and articular cartilage were 0.48-0.74, 0.83-1.15, and 1.76-2.53, respectively.

**Gatifloxacin: Maternal-Fetal Transfer and Excretion in Breast Milk in Rats** (BMS Report No. 910072415)

N. Koseki, C. Toriumi, Y. Nagatsu, H. Ohkubo (Kyorin Pharmaceutical Co., Japan)

Report dated: 11/16/98

Vol. 56, pp. 78-94

**Summary:** A 10 mg/kg single oral dose of  $^{14}\text{C}$ -gatifloxacin (Lot No. R0X9542, diluted with nonradiolabeled Lot G955320, 784 KBq/kg were given) was given to fasted female Wistar rats on day 18 of pregnancy to investigate transfer of radiolabeled compound to the fetuses. Three female rats each were sacrificed 1 and 24 hours after dosing and the amount of radiolabel in some maternal and fetal tissues (from 3 fetuses per dam) was determined [redacted]

The amounts (mean  $\pm$  SE) of radiolabel ( $\mu\text{g}$  equivalents/g or ml) detected 1 hour after administration of gatifloxacin were as follows:

<u>Maternal:</u>		<u>Fetal:</u>	
Blood	[redacted]	Whole fetus	2.45 $\pm$ 0.04
Plasma	[redacted]	Liver	3.91 $\pm$ 0.06
Heart	4.92 $\pm$ 0.12		
Lung	4.58 $\pm$ 0.05		
Liver	10.01 $\pm$ 0.30		
Pancreas	10.35 $\pm$ 0.80		
Spleen	7.52 $\pm$ 0.32		
Kidney	15.33 $\pm$ 2.05		
Adrenal	5.38 $\pm$ 0.13		
Placenta	3.76 $\pm$ 0.08		
Amnion	8.15 $\pm$ 0.06		
Am. Fluid	0.45 $\pm$ 0.02		
Ovary	3.33 $\pm$ 0.21		
Uterus	5.48 $\pm$ 1.17		

Twenty four hours after administration of drug, the amounts of gatifloxacin remaining in these tissues had fallen dramatically. In the majority, the  $\mu\text{g}$  equivalents of drug per g or ml had fallen to 0.05 or below. The exceptions were spleen (0.19  $\pm$  0.04), kidney (0.09  $\pm$  0.03), and amnion (0.11  $\pm$  0.02). The data indicate a low potential for accumulation in the tissues studied.

To investigate the extent to which gatifloxacin is secreted in rat breast milk, a single oral 10 mg/kg dose of <sup>14</sup>C-gatifloxacin (as above) was given to fasted female Wistar rats on day 10 of lactation. Blood and breast milk were collected 0.5, 1, 3, 5, 8, and 24 hours after dosing. Each lactating dam was housed with 3 pups and oxytocin (0.3 units per mouse) was given intraperitoneally about 5 minutes before milk was sampled to stimulate secretion. [redacted] solubilization of blood and milk (and decolorization of blood) was used to measure the amount of radiolabel in the samples.

The amounts (mean ± SE) of gatifloxacin (µg equivalents/ml- blood or g- milk) in blood and breast milk at various times following administration of drug were:

	<u>Blood:</u>	<u>Milk:</u>
0.5 hr	1.01 ± 0.32	3.39 ± 0.87
1 hr	1.02 ± 0.20	4.30 ± 1.31
3 hr	0.68 ± 0.08	3.32 ± 0.79
5 hr	0.50 ± 0.06	3.63 ± 0.25
8 hr	0.24 ± 0.04	1.35 (only 2 samples due to error)
24 hr	0.08 ± 0.01	0.05 ± 0.05 (detected in milk of 1/3 rats)

Gatifloxacin crossed the placenta and was found in rat fetuses after oral maternal dosing. Additionally, the drug is secreted into the breast milk of lactating rats and was present in a higher level in breast milk than in maternal blood.

**BMS-206584: Oral Toxicokinetics Study in Pregnant Rabbits, Kyorin Study No. A98EU07 (BMS Report No. 910072260)**

S. Kudo, M. Yamasaki, T. Okamura, C. Matsumoto, M. Sekine, T. Takahashi, K. Tsuru (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 9/22/98 (Kyorin)

Vol. 56, pp. 95-153

**Summary:** This toxicokinetics study was performed in pregnant Kbl:JW rabbits to supplement the teratology (Segment 2) study conducted in this species. Pregnant female rabbits received daily oral 50 mg/kg doses of gatifloxacin (Lot No. G715321) in 0.3% carboxymethyl cellulose during days 6-18 of gestation. Blood samples were drawn on the first and final days of dosing 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after drug was administered. Additionally, a blood sample was drawn prior to the administration of the final gatifloxacin dose. Only data from rabbits confirmed to be pregnant by a cesarean section performed on day 19 of gestation were utilized, giving a total of 7 females (out of 8 copulated females). No deaths or abortions occurred during the dosing period and reduced body weights and food consumption were observed in several animals, consistent with the observations from the Segment 2 study. Plasma from the rabbits was frozen at -20°C and sent to Bristol-Myers Squibb for analysis [redacted]

T<sub>max</sub> was between 0.5 and 2 hours on days 6 and 18, with the average being about 1 hour. The average ( $\pm$  SD) C<sub>max</sub> on days 6 and 18 was similar ( $8.88 \pm 2.38 \mu\text{g/ml}$  and  $9.67 \pm 2.47 \mu\text{g/ml}$ , respectively). However, the mean AUC<sub>0-24 hr</sub> for day 18 ( $66.1 \pm 38.7 \mu\text{g}\cdot\text{hr/ml}$ ) was about twice as great as for day 6 ( $34.8 \pm 7.5 \mu\text{g}\cdot\text{hr/ml}$ ). The largest increases came in 2 rabbits, with more modest increases in the rest.

**Intraocular Pharmacokinetics of Gatifloxacin in Pigmented Rats (BMS Study No. 910070168)**

S. Izawa, M. Komuro, F. Taga (Kyorin Pharmaceutical Co., Japan)

Report dated: 6/10/98

Vol. 56, pp. 154-175

**Summary:** Male Long-Evans rats (8 weeks old) received a single oral 20 mg/kg dose of <sup>14</sup>C-gatifloxacin (Lot No. CFQ8394 diluted with nonradiolabeled Lot No. G0X5321, 0.58 Mbq/kg) or 14 consecutive daily doses at the same level. For the single dose, blood samples were collected from 3 rats per time point 1, 2, 4, 6, 8, and 24 hours after administration. They were solubilized and decolorized for [redacted]. Plasma was also solubilized for [redacted]. Additionally, 3 rats per time point were sacrificed by exsanguination 1 and 24 hours and 1, 4, and 12 weeks after dosing. Ocular tissues were frozen and separated for [redacted] following combustion and plasma samples were also solubilized and counted. For the multiple dose study, blood samples were collected from 4 rats per time point 1, 2, 4, 6, 8, and 24 hours after drug was administered on days 1, 7, and 14, with samples also taken before dosing on days 7 and 14. Four rats per time point were sacrificed by exsanguination 1 and 24 hours and 1, 4, 12, 24, 36, and 48 weeks after the final dose of gatifloxacin was administered. Tissues were harvested for [redacted] as above.

The highest concentration of gatifloxacin in blood (about 1.6-1.9  $\mu\text{g eq/ml}$ ) was found 1 hour after dosing after either single or multiple doses of the drug. Radiolabel was no longer detected in blood or plasma 24 hours after either the single dose or multiple gatifloxacin doses. Radiolabel was not detected in the cornea or lens after the single dose of gatifloxacin. It was not detected in cornea after multiple dosing either, and only a small amount was detected in lens 24 hours after the last dose was given, but not at any other time. The greatest amounts of gatifloxacin were found in the pigmented ocular tissues, and the drug stayed bound to these tissues for long periods of time, even after the single dose. The binding did not appear to be irreversible and the drug was eliminated from the pigmented ocular tissues slowly over time. However, gatifloxacin was still detected in the iris/ciliary body and retina/choroid of pigmented rats 12 weeks after a single 20 mg/kg dose and 48 weeks after 14 consecutive 20 mg/kg daily doses.

**Mean Gatifloxacin Levels in Ocular Tissues and Blood  
After a Single Dose or Repeated Dosing ( $\mu\text{g eq/ml or g}$ )**

	Blood	Plasma	Cornea	Iris/ Ciliary Body	Lens	Vitreous Body	Retina/ Choroid	Sclera
Single								
1 hr			ND*	16.4	ND	0.57	13.7	2.63
24 hr			ND	78.6	ND	0.75	33.2	5.86
1 w			ND	47.3	ND	ND	20.4	2.32
4 w			ND	37.3	ND	ND	9.15	2.09
12 w			ND	21.2	ND	0.25	4.65	0.97
Repeat								
1 hr			ND	544	ND	1.85	164	36.9
24 hr			ND	606	0.14	2.73	159	30.6
1 w			ND	490	ND	1.20	119	22.4
4 w			ND	301	ND	0.19	74.4	11.3
12 w			ND	162	ND	ND	26.8	4.31
24 w			ND	87.7	ND	ND	8.17	0.37
36 w			ND	28.3	ND	ND	3.23	0.22
48 w			ND	25.1	ND	ND	3.24	0.26

\*Not Detected

**Mass Balance, Absorption, and Disposition Study of [ $^{14}\text{C}$ ]Gatifloxacin (BMS-206584) in Male Dogs, Study No. 744/206584/001 (BMS Report No. 910070237)**

E. Gupta, F. LaCreta, V. Richie (Bristol-Myers Squibb, Princeton, NJ)

Report dated: 9/28/98

Vol. 58, pp. 1-46

**Summary:** Fasted male beagle dogs (n=3) were given single oral 12 mg/kg doses of  $^{14}\text{C}$ -gatifloxacin (Lot No. CFQ8394, diluted with nonradiolabeled Batch No. 07Z5020, 5  $\mu\text{Ci/kg}$ ). Blood samples were collected pre dose and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after dosing. Urine samples were collected at intervals 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, and 120-144 hours after dosing and fecal samples were collected at intervals 0-24, 24-48, 48-72, 72-96, 96-120, and 120-144 hours after dosing. Plasma and urine samples were analyzed for total radioactivity [redacted] and for gatifloxacin concentration using a [redacted]. Fecal and whole blood samples were analyzed only for total radioactivity after combustion.

The  $T_{\text{max}}$  for gatifloxacin concentration and the high level of total radioactivity in the plasma were both 2 hours (range of 0.5 to 2 hrs). The  $C_{\text{max}}$  for gatifloxacin was 5.26  $\mu\text{g/ml}$  and for total radioactivity was 6.95  $\mu\text{g eq/ml}$ . The  $\text{AUC}_{0-\infty}$  for gatifloxacin was 56.2  $\mu\text{g}\cdot\text{hr/ml}$  and for

total radioactivity was 70.2  $\mu\text{g eq}\cdot\text{hr}/\text{ml}$ . The half life for gatifloxacin was 8.3 hours and for total radioactivity was 9.3 hours. Gatifloxacin clearance was 15.9 ml/min. This suggests that tubular reabsorption occurs as the glomerular filtration rate in the dog is about 60 ml/min and gatifloxacin is about 15% protein bound in this species. The percentage of the dose excreted in the urine as unchanged gatifloxacin was 34.7%. The percentage of total radioactivity excreted in the urine was 47.0% and in feces was 39.9%. The data suggest that the majority of the radiolabel detected in the plasma and in the urine was unchanged gatifloxacin. The total fraction of the dose recovered during the 144 hour sampling period was 87%.

### Toxicology:

#### **Repeat Dose Studies:**

The data from the studies in this section were used for dose-setting for longer term studies (ultimately, the dietary carcinogenicity studies) in mice and rats. They are not considered pivotal studies. The reviews for the dietary carcinogenicity studies have been filed previously.

**BMS-206584: Two-Week Dietary Range-Finding Study in Mice, Study No. 2201 (167-001)**  
(BMS Report No. 910070405)

Report dated: 9/20/93, Japanese GLP

Vol. 11, pp. 1-73

**Summary:** Male and female B6C3F<sub>1</sub> mice (6 weeks old, 10/sex per dose group) were given gatifloxacin in their diet

at concentrations of 0 (control), 0.25, 0.5, 1.0, or 2.0%. The mean daily drug intake at each concentration of gatifloxacin for males was 561, 1074, 2336, and 3473 mg/kg and for females was 674, 1310, 2532, and 4695 mg/kg. Animals were fed the diet for 2 weeks prior to sacrifice and gross necropsy.

None of the animals in the 2% groups survived for the entire study. All animals were sacrificed in moribund condition between days 3 and 12 of dosing. The mice in this high dose group exhibited clinical signs such as wasting, piloerection, low body temperature, poor grooming of fur, decreased spontaneous motor activity, and dyspnea (females only). Several males in the 1% dose group demonstrated piloerection, but all mice in this group survived the study period. One male in the 0.5% group was found dead on day 14.

Suppression of body weight gain was clearly related to the dose of gatifloxacin. Mice fed diet with 2 or 1% gatifloxacin lost weight over the course of the study. Those in the 0.5 and 0.25% groups gained significantly less weight than controls, though the effect at 0.25% was less. Food consumption was lower than control in all gatifloxacin groups on the second day of the experiment, but only the 2% group had significantly lower food consumption than controls during the rest of the study period, with sporadic decreases at 1%.

Absolute weights of several organs were lower in the drug-treated mice than controls, and relative organ weights of the spleen, heart and liver were lower in the 0.25 and 0.5% gatifloxacin groups. Tissues were not examined microscopically, but gross changes were observed. "Whitish change" of the mesenteric lymph nodes occurred in a dose-responsive manner. Cecal dilatation was observed in all gatifloxacin dose groups and dilatation of the small intestine was in males at 0.5% and higher and in females from all gatifloxacin groups. Pale spleen occurred in each group of drug-treated mice in a dose-responsive manner. Pale liver was seen in drug-treated female mice, especially in the 0.5 and 1% dose groups. Many females in the 1% group had thymic atrophy. Small uteri were observed in a dose-responsive manner in drug-treated female mice and this observation was present in all females at 1%.

The investigators concluded that the maximum dose level of gatifloxacin for a 13-week dietary study in mice should not exceed 0.3-0.4%.

**BMS-206584: Three-Month Dietary Range-Finding Study in Mice (I), Study No. 2223 (167-002) (BMS Report No. 910070406)**

Report dated: 2/28/94, Japanese GLP

Vol. 11, pp. 74-161

**Summary:** Male and female B6C3F<sub>1</sub> mice (6 weeks old, 10/sex per dose group) were given gatifloxacin in their diet

at concentrations of 0 (control), 0.1, 0.2, or 0.4%. The mean daily drug intake at each concentration of gatifloxacin for males was 172, 362, and 764 mg/kg and for females was 219, 451, and 911 mg/kg. Mice were fed the diet for 13 weeks prior to sacrifice and necropsy.

Drug-related mortality was observed in every dose group. In the 0.1% group, 3 male were found dead or sacrificed moribund during weeks 8-11. In the 0.2% group, 1 male and 1 female mouse died during weeks 13 and 8, respectively. At 0.4%, 2 males and 2 females were found dead or moribund during weeks 6-13. Two other animals in the 0.1 and 0.2% dose groups appeared moribund at the time of scheduled sacrifice. Clinical signs such as piloerection, low body temperature, poor grooming of fur, decreased spontaneous motor activity, and dyspnea were seen in some animals that were sacrificed in moribund condition.

Suppression of body weight gain was clearly related to the dose of gatifloxacin. Mice fed diet with 0.4% gatifloxacin exhibited suppression of body weight gain beginning during weeks 2-3. At the end of the study, the males in the 0.4% group weighed 14.5% less than controls and the females weighed 9.9% less than controls. Males from the 0.2 and 0.1% groups showed suppression of body weight gains beginning during weeks 5 and 10, respectively. The males in these dose groups weighed 8.7% and 14.2% less than controls by the end of the study. The female mice in the 0.2 and 0.1% gatifloxacin groups had similar body weight gain to controls. Food consumption was not lower than control in the drug-treated mice and, overall, it was significantly greater in the males fed a diet containing 0.4% gatifloxacin.

Absolute weights of several organs were slightly lower in the drug-treated mice (particularly the 2 higher dose groups) than controls. Overall, relative organ weights did not differ much between treatment groups. Gross changes observed at necropsy included cecal dilatation in 12-14 mice from each gatifloxacin group and ileocecal volvulus (cecal torsion) in 14-17 mice from each gatifloxacin group. These gross findings were also seen in all of the mice sacrificed in moribund condition as well as at scheduled sacrifice. Histopathologic changes associated with gatifloxacin were present in the cecum and observed in all dose groups. These included epithelial degeneration, muscular hypertrophy, ulcer, hemorrhage, congestion, edema, and cellular infiltration.

The investigators concluded that this study did not identify optimal dose levels for a mouse dietary carcinogenicity study as drug-related deaths were seen even in the lowest dose group, the 0.1% gatifloxacin dietary admixture.

**BMS-206584: Three-Month Dietary Range-Finding Study in Mice (II), Study No. K92GM02 (BMS Report No. 910070279)**

S. Imai, S. Ohtake, Y. Haga, Y. Masumoto, T. Toriyabe, K. Tateyanagi, H. Tanase, S. Iwasaki, Y. Sato (Kyorin Pharmaceutical Co., Tokyo and Tochigi, Japan)

Report dated: 10/20/94, Japanese GLP

Vol. 11, pp. 162-197

**Summary:** This study was a second attempt to identify appropriate doses for a mouse carcinogenicity study. Male and female B6C3F<sub>1</sub> mice (6 weeks old, 10/sex per dose group) were given gatifloxacin in their diet [redacted] at concentrations of 0 (control), 0.05, 0.12, or 0.3%. The mean daily drug intake at each concentration of gatifloxacin for males was 93, 246, and 591 mg/kg and for females was 122, 293, and 744 mg/kg. Mice were fed the diet for 13 weeks prior to sacrifice and necropsy. Each gatifloxacin group had 27 extra mice for toxicokinetic analysis (results reported elsewhere). Blood samples were collected for 3 mice/sex per group at 4 hour intervals during a 24 hour period in the second week of gatifloxacin exposure and at 9 AM and 5 PM on one day during week 12.

One male mouse in the 0.12% group was sacrificed in moribund condition during the 12<sup>th</sup> week of administration. This animal exhibited ptosis, piloerection, decreased spontaneous activity, emaciation, and decreased body temperature. At necropsy, cecal torsion with hemorrhage was observed. Microscopic changes of the cecum in this mouse included mucosal necrosis, edema, and leukocyte infiltration. The remaining animals survived until scheduled sacrifice.

Body weight gain compared to controls was inhibited in a dose-dependant manner in the male mice. In the 0.05, 0.12, and 0.3% dose groups, body weight gains were 6.7%, 12%, and 12.6% less than controls, respectively. In the female mice, however, body weight gain amongst all groups of mice was similar to control. Food intake was decreased transiently on days 1 and 2 in all gatifloxacin groups, but over the remainder of the study, no difference from control was seen.

Absolute weights of several organs were slightly lower in the drug-treated mice (particularly the 2 higher dose groups) than controls. Overall, relative organ weights did not differ much between treatment groups. Cecal weights were measured in this study and the absolute and relative weight of this organ was higher in the drug-treated mice (again, especially in the 2 higher dose groups) compared to control. Cecal dilatation was observed grossly in 15-20 mice from each gatifloxacin group and cecal convolution (helical turns in cecum, but not torsion) was seen in 17-19 mice from each gatifloxacin group. Histopathologic changes were not observed in the cecae of mice that survived until scheduled sacrifice.

The investigators concluded that the highest percentage of gatifloxacin that should be put into the feed for the mouse dietary carcinogenicity study should be approximately 0.05%, perhaps slightly more.

**BMS-206584: Two-Week Dietary Range-Finding Study in Rats, Study No. K92GR01 (BMS Report No. 910070389)**

Y. Nomoto, Y. Haga, S. Ohtake, H. Tanase, S. Takano (Kyorin Pharmaceutical Co., Tokyo, Japan)

Report dated: 5/29/92, Japanese GLP

Vol. 11, pp. 198-220

**Summary:** Male and female F344/DuCrj rats (6 weeks old, 5/sex per dose group) were given gatifloxacin in their diet [redacted] at concentrations of 0 (control), 0.125, 0.25, 0.5 or 1%. The mean daily drug intake at each concentration of gatifloxacin for males was 102, 204, 385, and 561 mg/kg and for females was 97, 195, 370, and 576 mg/kg. Rats were fed the diet for 14 days prior to sacrifice and necropsy. Each gatifloxacin group had 30 extra male rats for toxicokinetic analysis (results reported elsewhere). Blood samples were collected for 5 per group at six 4 hour intervals beginning at 11 AM during days 10-11 of gatifloxacin exposure.

No animals died during the administration period and no abnormal clinical signs were observed.

Body weight gain compared to controls was inhibited in a dose-dependant manner in the male rats. In the 0.25, 0.5, and 1% dose groups, body weight was significantly less than control at the end of the study. The male rats in the 1% dose group weighed almost 30% less than controls and those in the 0.5% group weighed about 12% less than controls. In the female rats, only the mean body weight of the 1% dose group was significantly less than control at the end of the study (approximately 17% less). Food intake was decreased by close to 50% in the 1% dose group compared to control during the study. The rats in the other gatifloxacin groups tended to consume slightly less food than controls during the study period.

Gross necropsy of the rats revealed no abnormalities other than enlarged cecae. This was observed in rats from all of the gatifloxacin dose groups.

The investigators concluded that the highest dose to be used for a 3 month rat dietary study with gatifloxacin should be between 0.5-1%, but not exceeding 1%, based upon the body weight gain and food consumption data.

**BMS-206584: Three-Month Dietary Range-Finding Study in Rats, Study No. K92GR03  
(BMS Report No. 910070278)**

Y. Nomoto, Y. Haga, S. Ohtake, H. Tanase, Y. Masumoto, T. Toriyabe, K. Tateyanagi (Kyorin Pharmaceutical Co., Tokyo, Japan)

Report dated: 3/10/93; Japanese GLP

Vol. 14, pp. 1-48

**Summary:** Male and female F344/DuCrj rats (5 weeks old, 10/sex per dose group) were given gatifloxacin in their diet ~~at~~ at concentrations of 0 (control), 0.05, 0.13, 0.3 or 0.8%. The mean daily drug intake at each concentration of gatifloxacin for males was 32, 85, 194, and 636 mg/kg and for females was 33, 87, 197, and 547 mg/kg. Rats were fed the diet for 90 days prior to sacrifice and necropsy. The 0.13 and 0.8% gatifloxacin groups had 12 extra rats/sex for toxicokinetic analysis. Blood samples were collected for 3/sex per group at 2 time points (morning and afternoon) during weeks 6 and 10 of gatifloxacin exposure.

One male rat in the 0.8% group was found dead on day 71 of administration. This animal exhibited piloerection, abdominal swelling, emaciation, and exposures glans penis prior to its death. At necropsy, cecal congestion and enlargement were observed. The nine other males in this group were sacrificed on day 72 of administration because they were exhibiting some of the same clinical signs as the dead rat and the investigators did not believe that they would survive until scheduled sacrifice. No mortality occurred in female rats from this group, but all of them exhibited abdominal swelling and half had piloerection beginning during week 12. Water intake was higher in the 0.8% dose group than in the lower dose groups. Abnormal clinical signs were not observed in the lower dose groups.

Body weight gain in the male rats was reduced compared to control in the 0.13, 0.3, and 0.8% groups, but only the two higher groups were statistically significantly different from control. At the time that they were sacrificed on day 72, the mean body weight of the male rats in the 0.8% group was 51% less than controls. At the time of scheduled sacrifice, the mean body weight of the 0.3% and 0.13% dose groups were 10.6% and 6.2% less than control, respectively. Only the female mice in the 0.8% group gained significantly less body weight than controls. The mean body weight of this group was 16% less than control at the time of scheduled sacrifice. Food consumption was significantly less than control in the 0.8% gatifloxacin group, especially during the first few weeks of the study. In males, consumption recovered slowly toward control values after 3 weeks, but it never reached control levels (0.8% males ate about 12.5-14.5 g of food daily compared to about 14-17 g for controls.) In females, food consumption in the 0.8% group returned to control levels after the first month of the study.

Serum clinical chemistry values at the time of sacrifice showed significant decreases in total protein, phospholipid, and cholesterol in the 0.3 and 0.8% dose groups. Decreased albumin was seen at 0.8%. Increased blood glucose (approximately 500 mg/dl, about 3 times control) was seen at 0.8%. Alkaline phosphatase levels in the 0.8% group were about 1000 IU/l, approximately twice as high as controls. Serum alkaline phosphatase was more modestly elevated in the other gatifloxacin dose groups.

Liver and kidney weights of the rats were measured at necropsy. Absolute liver weights in the rats receiving  $\geq 0.13\%$  dietary gatifloxacin were significantly lower than control (especially high dose males whose mean liver weight was about half of control), but changes in relative liver weights were modest, including the high dose males. Decreased absolute kidney weights and increased relative kidney weights seen in the 0.8% rats appeared to be more reflective of reduced body weight gain than indicative of a renal effect.

At necropsy, enlarged cecum was observed in all gatifloxacin-treated rats. In the high dose group, a whitish discoloration of the jejunal mucosa was observed in all rats; microscopic evaluation of this tissue revealed a foamy degeneration of the villous epithelium. Atrophy of the prostate, seminal vesicles, and uterus were seen in all rats from the 0.8% group, as applicable. Vacuolation of the pancreatic  $\beta$ -cells was observed in all rats at 0.8% gatifloxacin. Other microscopic changes observed in the 0.8% group included increase of fatty droplets in hepatocytes (9/10 males, 9/10 females) and vacuolar degeneration of distal tubular epithelium of kidney (10/10 males, 9/10 females). Increased fatty droplets in hepatocytes was also seen in 7/10 males in the 0.3% group, but not females. Femurs from 3 male and female rats in the control and 0.3% dose groups and 3 females from the 0.8% group were decalcified and the distal ends examined microscopically after staining with hematoxylin and eosin. Osteogenesis was decreased in the metaphyses of the bones from the 0.8% females (males not sampled), but the chondrocyte column had a regular arrangement. No changes in the bone were observed in the males and females from the control or 0.3% groups.

During week 10, the serum concentrations of gatifloxacin in the 0.8% rats were  $8.95 \pm 1.23$   $\mu\text{g/ml}$  (morning) and  $8.21 \pm 2.56$   $\mu\text{g/ml}$  (evening). Data from the other groups were not provided.

The investigators concluded that the highest dose to be used for a rat dietary carcinogenicity study with gatifloxacin should be between 0.13-0.3%, but not exceeding 0.3%, based upon the body weight gain and food consumption data. Gross and microscopic changes observed in the drug-treated animals (especially at the high dose group) were consistent with those seen in other experiments in rats with gatifloxacin.

### **Reproduction and Developmental Toxicity Studies:**

The data from the pilot studies in this section were used for dose-setting for the pivotal reproduction toxicity studies in rats and rabbits. The reviews for the pivotal reproduction toxicity studies have been filed previously.

### **BMS-206584: Preliminary Oral Study of Fertility and Early Embryonic Development in Rats, Study No. C90FRA6 (BMS Report No. 910070421)**

A. Murayama, H. Suzuki (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 10/8/90, not GLP

Vol. 24, pp. 1-67

**Summary:** Male and female Wistar rats (10 weeks old, 6/sex per group) received 0 (0.3% carboxymethyl cellulose vehicle control), 50, 100, or 200 mg/kg of gatifloxacin daily via oral gavage. Rats received drug beginning 14 days prior to the initiation of mating with males continuing to receive drug until the end of the 14 day mating period and females continuing to receive drug until day 7 of gestation. Male and female animals were paired 1:1 within the same dose group for up to 14 days. Day 0 of gestation was the day that a female expelled a copulatory plug or had sperm present in a vaginal smear. Food [redacted] and filtered well water were available *ad libitum*. Males were sacrificed at the end of the 14 day mating period and females were sacrificed on day 20 of pregnancy.

One female rat from the 200 mg/kg group died during the mating period and another female from the 100 mg/kg group died on day 4 of gestation. Gross necropsy revealed that these deaths were due to dosing accidents. No other mortality was observed during the study. One male in the 200 mg/kg group had soft stool on day 9 of administration, but no other abnormal clinical signs were seen.

In the male rats, there was a tendency for body weight gain to be lower in the gatifloxacin-treated animals compared to controls; however, the differences in mean body weight over the course of the study were only sporadically statistically significant. The mean body weights for male rats at the end of the study were not statistically different between control and drug-treated rats, but the mean body weight of the controls was  $447.0 \pm 26.4$  g and the mean body weight of the 200 mg/kg males was  $417.7 \pm 12.4$  (about 6.5% less than control). In female rats, there was no difference in body weight gain among the treatment groups. During the first 3 days of dosing, the gatifloxacin-treated rats ate significantly less food than controls, but food consumption rose back to control levels thereafter.

Male rats treated with gatifloxacin demonstrated enlarged cecae at the time of necropsy.

In the control group, 5/6 rat pairs mated within the 14 day mating period and 4/5 of the females were pregnant. In the gatifloxacin groups, all surviving rats mated and were pregnant. Gatifloxacin treatment did not affect the number of corpora lutea, and it did not appear to be associated with pre- or post-implantation loss. In fact, the preimplantation loss in the gatifloxacin-treated rats was much less than controls (e.g., about 2% in the 200 mg/kg group), but it should be noted that the rate of preimplantation loss in the control group was very high (about 50%). The mean litter sizes in the gatifloxacin groups were greater than control due to the differences in preimplantation loss. The mean fetal and placental weights in the gatifloxacin group were less than control, but this was probably due to the litter size disparity. Drug-related skeletal or visceral malformations were not observed, but delayed ossification of vertebrae and limbs was seen at 200 mg/kg.

The investigators concluded that 200 mg/kg was an appropriate high dose for the pivotal rat fertility and early embryonic development study. The reviewer believes that a slightly greater high dose (e.g., 250-300 mg/kg) could have been used.

**BMS-206584: Preliminary Oral Study of Embryo-Fetal Development in Rats, Study No. C91TRA2 (BMS Report No. 910070419)**

H. Suzuki, A. Omotera, H. Morihara (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 6/26/91, not GLP

Vol. 24, pp. 119-178

**Summary:** Presumed pregnant female Wistar rats (11 weeks old, 10 per group) received 0 (0.3% carboxymethyl cellulose vehicle control), 200, 300, or 400 mg/kg of gatifloxacin daily via oral gavage from days 7-17 of gestation. Food [ ] and filtered well water were available *ad libitum*. Three rats per group were allowed to spontaneously deliver their litters (culled to 4 pups/sex on day 4) and were observed until their sacrifice on day 7 of lactation. The remaining 7 rats per dose group underwent cesarean section and sacrifice on day 20 of gestation.

None of the rats died during the course of the study. The only clinical sign observed was a bloody vaginal discharge from 2 females in the 400 mg/kg group on days 16 and/or 17 of gestation.

In the 400 mg/kg rats, body weight gain was significantly less than control. At the time of cesarean section, these rats weighed almost 14% less than controls. Throughout most of the treatment period, these rats consumed significantly less food than controls, as well. On several days during the treatment period, the rats in the other 2 gatifloxacin groups also consumed significantly less food than controls. Those rats also weighed less than controls at the time of cesarean section, but the difference was not statistically significant though the reduction did appear dose-related.

Cecal enlargement was seen in 2/7 dams in the 300 mg/kg group and 5/6 dams at 400 mg/kg at the time of cesarean section. One rat each in the control and 400 mg/kg groups was not pregnant.

Of the 6 pregnant rats in the at 400 mg/kg, 2 had no live fetuses (only placental remnants remained after resorption) and the overall postimplantation loss for this group was 72%.

The fetuses from gatifloxacin-treated dams that underwent cesarean section had lower body weights and lower placental weights than controls. Due to variability among the relatively small number of animals used for this study, the difference for fetuses was statistically significant for males only at 200 mg/kg and both genders at 300-400 mg/kg and the difference for placenta was statistically significant only at 400 mg/kg. The reviewer believes the difference from control to be of biological significance at all dose levels for both genders. Bent radius/ulna was seen in a greater percentage of drug-treated fetuses than controls. The percentage of fetuses (per total, not per litter) with this malformation was 0% in the control group and 4.7%, 8%, and 24.2% in the 200, 300, and 400 mg/kg dose groups, respectively. A bent scapula was seen in one fetus at 400 mg/kg. There was a dose-related increase in the percentage of fetuses exhibiting retarded ossification of several bones (including occipital, intraparietal, sternbrae, phalanges). All gatifloxacin-treated groups were affected. The percentage of fetuses with wavy ribs was also higher in the gatifloxacin-treated litters than controls.

Of the dams which were assigned to the spontaneous delivery group, one rat in the 400 mg/kg group had not delivered by day 24 of gestation. This animal was sacrificed, necropsied, and its uterus contained nothing but early resorptions. The other dams all delivered their fetuses. The 2 remaining dams in the 400 mg/kg group had smaller litters than control, as did the 3 dams from the 300 mg/kg dose group. Pups in the 300 and 400 mg/kg dose groups weighed significantly less than control at birth, but appeared to be catching up to controls over the next several days. Their weights had not achieved control levels by lactation day 7 when they were sacrificed, but the weight differences were no longer statistically significant. Survival rates from birth to day 4 were 100% for all rats except the females in the 300 mg/kg group which had a

72.2% survival rate. The time of ear opening in the pups did not differ among the treatment groups.

The investigators concluded that the highest appropriate dose to be used in the pivotal rat teratology study should be less than 200 mg/kg due to the reduced food consumption and body weight gain observed in the dams. The dose chosen for the pivotal study was 150 mg/kg. The dams in the pivotal study ate slightly less food than controls, but their body weight gain was not suppressed. Signs of fetotoxicity (reduced fetal and placental weights) were observed in this group, but no visceral or skeletal malformation were seen (review of this study is in [redacted] [redacted])

**BMS-206584: Preliminary Intravenous Study of Embryo-Fetal Development in Rats, Study No. C92TRA1 (BMS Report No. 910070420)**

H. Suzuki, T. Tsuchiya, A. Omotera, H. Morihara (Kyorin Pharmaceutical Co., Tochigi, Japan)

Report dated: 12/26/92, not GLP

Vol. 29, pp. 1-75

**Summary:** Presumed pregnant female Wistar rats (11 weeks old, 10 per group) received 0 (physiological saline control), 15, 30, or 60 mg/kg of gatifloxacin daily via IV bolus from days 7-17 of gestation. Food [redacted] and filtered well water were available *ad libitum*. Three rats per group were allowed to spontaneously deliver their litters (culled to 4 pups/sex on day 4) and were observed until their sacrifice on day 7 of lactation. The remaining 7 rats per dose group underwent cesarean section and sacrifice on day 20 of gestation.

One rat from the control group died on day 19 of gestation. Necropsy revealed no abnormal findings. No clinical signs of toxicity were observed in any of the dams.

Body weight gain was not significantly less than control for dams in any gatifloxacin dose group, though rats in the 60 mg/kg group did tend to gain less body weight than controls during the dosing period. Food consumption was significantly less than control in the gatifloxacin-treated rats on one day near the beginning of the period of drug administration. In general, although the drug-treated rats tended to consume slightly less food than controls, the difference was relatively small and was not statistically significant except on the occasion mentioned above.

Necropsy did not reveal any gross abnormalities in any of the dams. One dam in each dose group, including control, was not pregnant.

Fetal body weights and placenta weights were similar between control and gatifloxacin-treated groups. Litter size was similar between the treatment groups and no drug-related post-implantation loss was observed. Bent scapula was seen in two fetuses at 60 mg/kg (2.2% of total fetuses). Deformed humerus was seen in one fetus from the 60 mg/kg group (1.1% of total fetuses). These skeletal malformations were not observed in any control fetuses or in any other gatifloxacin-exposed fetuses. There was a dose-related increase in the percentage of fetuses with wavy ribs in the gatifloxacin-treated litters compared to control.

No abnormalities during delivery or pup rearing were observed in the dams which were assigned to the spontaneous delivery group. Mean body weights of the pups were similar across treatment groups and litter sizes were also similar. Body weight gain during the 7 days of

lactation did not differ among the treatment groups. Survival rates from birth to day 4 were not less than control in the gatifloxacin-treated litters. The time of ear opening in the pups did not differ among the treatment groups.

The investigators concluded that the highest appropriate dose to be used in the pivotal rat teratology study should be 30 mg/kg based upon the results of this study. This was the dose chosen for the pivotal IV rat teratology study. The dams in the pivotal study had no clinical signs of toxicity at the 30 mg/kg dose level and neither food consumption nor body weight gain was less than control. Signs of fetotoxicity (wavy ribs and retarded ossification of sternbrae) were observed in this group, but no visceral or skeletal malformation were seen (review of this study is in [redacted]). The reviewer disagrees that the highest appropriate dose for the pivotal study should have been 30 mg/kg. The dose-setting study contained no data suggesting that 60 mg/kg was an inappropriately high dose for the dams or the fetuses. The reviewer cannot help but wonder whether the investigators chose 30 mg/kg over 60 mg/kg due to the skeletal malformations observed at the higher dose. This type of study is supposed to be performed to explore the potential for a compound to induce fetal malformations. The highest doses used should be set at the maximum tolerated dose for the dams unless a lower dose is necessary to obtain a sufficient number of fetuses for examination (e.g., very high pre- or post-implantation loss occurs at doses well tolerated by the dam). A dose should not be chosen based upon having observed fetal malformations in the dose setting study that one would prefer not to see during the pivotal teratology study. Based upon the data from this study, as well as the oral rat dose-setting study above, the reviewer believes that the skeletal malformations observed are probably drug-induced. The finding belongs in the label despite the negative results obtained in the pivotal studies where the high doses seem to have been set to avoid fetal malformations rather than unacceptably high toxicity to the dams.

**BMS-206584: Preliminary Oral Study of Embryo-Fetal Development in Rabbits, Study No. C91TUA4 (BMS Report No. 910070418)**

H. Suzuki, A. Omotera, H. Morihara (Kyorin Pharmaceutical Co., Central Research Laboratories, Tochigi, Japan)

Report dated: 1/8/92, not GLP

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**Summary:** Presumed pregnant female Kbl:JW rabbits (18 weeks old, 6 per group) received 0 (0.3% carboxymethyl cellulose vehicle control), 10, 40, 70, or 100 mg/kg of gatifloxacin daily via oral gavage from days 6-18 of gestation. Food [redacted] and filtered well water were available *ad libitum*. Blood samples were taken on day 17 or 18 of gestation from 2-3 rabbits per group to determine the serum concentration of gatifloxacin (except no samples were taken from the 100 mg/kg does). Does underwent cesarean section and sacrifice on day 29 of gestation.

One rabbit each in the control and 40 mg/kg groups was found not to be pregnant. One doe in the 70 mg/kg group was found dead on day 29. This rabbit was in the process of aborting its litter. Besides this doe, 2 others in the 70 mg/kg group and 5 in the 100 mg/kg group aborted