Pharmacokinetic Parameters:

Blood samples (approximately 4.5 mL) were taken at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8 and 12h post-dose (a 24-26h sample was taken if a corresponding blister fluid sample was collected). Blister fluid samples were taken pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8 and 12h post-dose (a 24-26 hour sample was taken if the blister was patent). Urine was collected pre-dose and 0-6, 6-12 and 12-24 hours post-dose. Samples were analyzed for gemifloxacin in human plasma, blister fluid and urine using a microbiological method

[̄] The lower limit of quantification for each of the assays for gemifloxacin was ⎯⎯⎯⎯ . All drug assays were performed in the ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯

Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}). Urinary excretion (Ae), was calculated for each collection period by multiplying the urine concentration by the total volume of urine collected in that period. Renal clearance, CLr, was calculated as the ratio of Ae_{24}/AUC_{0-inf}.

Reviewer's comment: The validation of microbiological assay method was not provided in this application. Due to the inability to differentiate parent and metabolites, bioassay is not usually accepted for pharmacokinetic study. This may be the reason for a slightly higher C_{max} and A_e in this study compared with other studies (See Pharmacokinetic Results).

Statistical Methods:

The primary endpoint was the concentration of gemifloxacin in blister fluid. There was no formal statistical analysis.

Pharmacokinetic Results:

Blisters were successfully raised in eight volunteers, but blisters in only five of these subjects provided enough inflammatory fluid throughout the day to allow adequate data for pharmacokinetic analysis. Figure 1 and Table 2 show plasma and blister fluid concentration-time profile of gemifloxacin and its relevant pharmacokinetic parameters. AUC_{0-inf} and C_{max} in blister fluid was 40 and 70% lower than in plasma, respectively. In 4 of 8 subjects who has blisters raised, concentrations of gemifloxacin in blister fluids at 30 minutes were lower than the lower limit of quantification, i.e. ⎯⎯⎯⎯⎯⎯ Similarly, median T_{max} in blister fluids was greater compared with plasma, i.e., 3 *vs* 1 hours. **Overall, the rate and extent of gemifloxacin penetration into blister fluid does not seem comparable with plasma.** However, similar $T_{1/2}$ between plasma and blister fluids, i.e., 5.94 *vs* 6.27 hours, indicates that gemifloxacin was eliminated from the inflammatory exudate at a similar rate as from plasma.
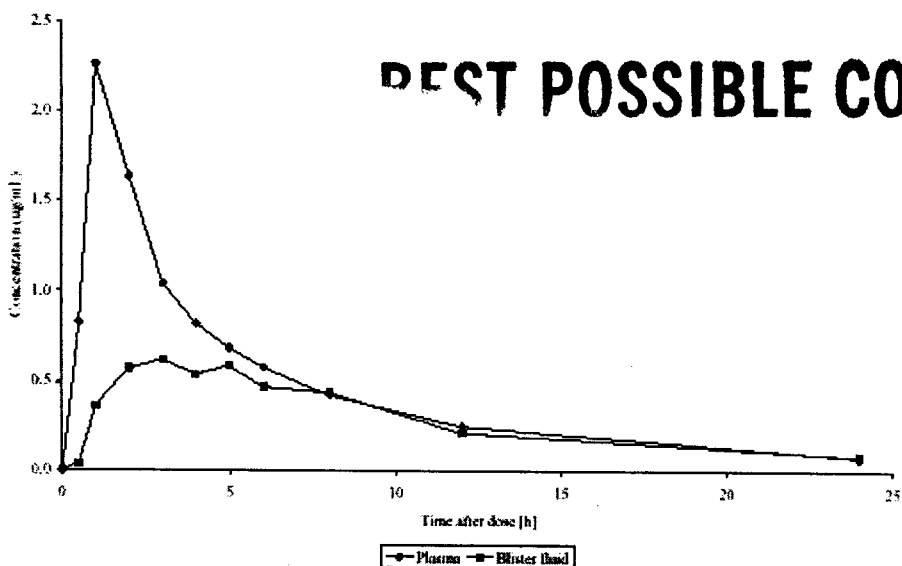
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Figure 1. Plasma (n=10) and blister fluid (n=5) concentration-time profiles of gemifloxacin at time up to 24 hours administration of a single oral dose of 320 mg gemifloxacin

Table 2. Pharmacokinetic parameters of gemifloxacin after single oral administration (320 mg)

	Plasma (n=10)	Blister fluid (n=8)	Ratio of blister fluid:plasma
C_{max} $(\mu g/mL)^a$	2.33±0.54 (1.51-3.03)	0.72±0.30 (0.30-1.12)	0.33±0.14 (0.136-0.517)
AUC_{0-inf} $(\mu g \cdot h/mL)^a$	11.0±2.12 (8.28-15.5)	6.63±2.33 $(4.61-10.2)^c$	0.61±0.10 $(0.491-0.756)^c$
T_{max} $(hour)^b$	1.00 (1.00-2.00)	3.00 (2.00-6.00)	—
$T_{1/2}$ $(hour)^a$	5.94±0.42 (5.22-6.68)	6.27±2.36 $(2.71-8.65)^c$	—
Ae_{24} (% dose)^a	36.1±7.5 (28.1-47.6)	—	—
CLr $(L/h)^a$	10.7±1.83 (6.66-12.7)	—	—

^{a}: Mean±SD, range; ^{b}:Median, range; ^{c}: n=5

Safety Results:
Two adverse events (AE's) were reported following treatment with study medication. One subject reported mild headache, the onset of which was one hour after the medication was administered, and which was suspected to be related to the study drug. A second subject reported mild injection site pain at the cannula site. Both AEs resolved by

the study end. There are no changes in vital signs, ECG, or clinical laboratory parameters during the study.

Conclusions:

a. Gemifloxacin penetration into blister fluid does not seem comparable with plasma.

b. Gemifloxacin was eliminated from the inflammatory exudate at a similar rate as from plasma.

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7. . <u>Study 033:</u> An open, randomized, two-treatment, four-period, replicated crossover study to demonstrate the bioequivalence in vivo of two batches of the commercial formulation tablet of gemifloxacin with differing dissolution profiles, in healthy volunteers

NDA Vol. 6.003 – 6.005, pp 1-717

*In the original submission of this NDA, the sponsor proposed a dissolution specification of Q= ——(NLT ——of label claim released). The OCPB reviewer recommended to change this dissolution specification to Q=——(NLT —— of label claim released), based on the dissolution data that was provided by the sponsor. This study was conducted to investigate if the differences in dissolution rate affect the in vivo bioavailability of gemifloxacin. The results showed that the commercial formulation of gemifloxacin 320 mg with a lower in-vitro dissolution profile (——released at 30 minutes) is bioequivalent to the commercial formulation of gemifloxacin with >——release at 30 minutes. Based on these results, the **dissolution specification of Q= ——(NLT ——of label claim released), originally proposed by the sponsor, is considered to be acceptable.***

Study Dates:
The first subject was screened on the 21st February 2000 and the first dose was administered on the 6th March 2000. The last dose was administered on the 12th April 2000 and the last study visit was on the 26th April 2000.

Objectives:
To demonstrate the in vivo bioequivalence of two batches of the commercial formulation tablet of gemifloxacin with differing dissolution profiles, in healthy volunteers.

Formulations:

Batch A: Gemifloxacin commercial formulation (320 mg tablets) — % release at 30 minutes (Batch no. N99112)

Batch B: Gemifloxacin commercial formulation (320 mg tablets) — release at 30 minutes (Batch no. N99114)

There are no differences in the formulations including their compositions. Both batches are the formulations for the commercial use.

Study Design:
This study was conducted to an open label, randomized, two-treatment, four-period, replicated crossover design in healthy male and female volunteers. Each volunteer participated in four sessions and was administered, in a randomized order, one single oral dose of 320 mg gemifloxacin of either batch with differing dissolution profiles. Each subject received each batch twice on separate dosing sessions. Doses were administered after an overnight fast. There was a washout period of at least five days between each dosing session.

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Study Population and Demographic Data:

93

A total of 22 healthy (12 males and 10 females) subjects were recruited for this study. Two subjects were withdrawn after two dosing sessions due to personal reasons unrelated to the study. One subject was withdrawn due to an adverse event of abdominal pain (See Safety Results). Key demographic data for all subjects who entered the study and received at least one dose of study medication are listed in the Table 1.

Table 1. Demographic data

Parameter	Age (years)	Weight (kg)	Height (m)
n*	22	22	22
Mean	35	74.8	1.75
SD	6.5	14.9	0.10
Range	22 - 47	53.7 – 107.6	1.62 – 1.92

* 22 Caucasian subjects

Safety Parameters:

Hematology, clinical chemistry and urinalysis parameters were measured pre-study, pre-dose and 24 h post dose on each dosing day and at follow-up. **Blood pressure and pulse** measurements were taken pre-study, pre-dose on each dosing day, 12 hours post dose and at follow-up. **Twelve lead ECG** measurements were taken pre-study, pre-dose and at 2h post-dose on each dosing day and at follow-up. **Adverse event** forms were completed pre-dose, 2, 12 and 24 hours post dose on each dosing day and at follow-up. **A drug screen** was conducted pre-study and randomly conducted pre-dose. For female volunteers, a HCG (urine or blood) **pregnancy test** was also conducted pre-study, pre-dose at each session and at follow-up.

Pharmacokinetic Parameters:

Blood samples for pharmacokinetic analysis (approximately 3 mL) were collected at pre-dose and at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32 and 48 h following dosing of gemifloxacin in each treatment period. Human plasma samples were assayed for gemifloxacin using a method based on ———— with ———— conducted at the ———————————————— . The samples were analyzed by ———————— analysis employing ————————————— (lower limit of quantification for gemifloxacin was ———————— using a 50 µL aliquot). The assay was linear with the range of ———————— The within and between-run precisions were acceptable ————— .

Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}).

Statistical Methods:

Point estimates and 90% confidence intervals were computed for the ratios, i.e., Batch B: Batch A. Equivalence was demonstrated if the 90% confidence intervals for the ratios of both AUC and Cmax were completely contained within the range 0.80 to 1.25.

Pharmacokinetic Results:

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Figure 1 and Table 2 show the plasma concentration profiles of gemifloxacin and its relevant pharmacokinetic parameters, respectively, after oral administration of two batches of the commercial formulation of gemifloxacin (320 mg) with different dissolution profiles. Table 2 also shows the statistical bioequivalence assessment based on primary pharmacokinetic endpoints. The 90% confidence intervals for the ratio of adjusted geometric means for the primary endpoints AUC_{0-inf} and C_{max} for gemifloxacin were completely contained within the equivalence range of 0.80 to 1.25, indicating that the two formulations are bioequivalent. On average, gemifloxacin T_{max} was similar for both formulations.
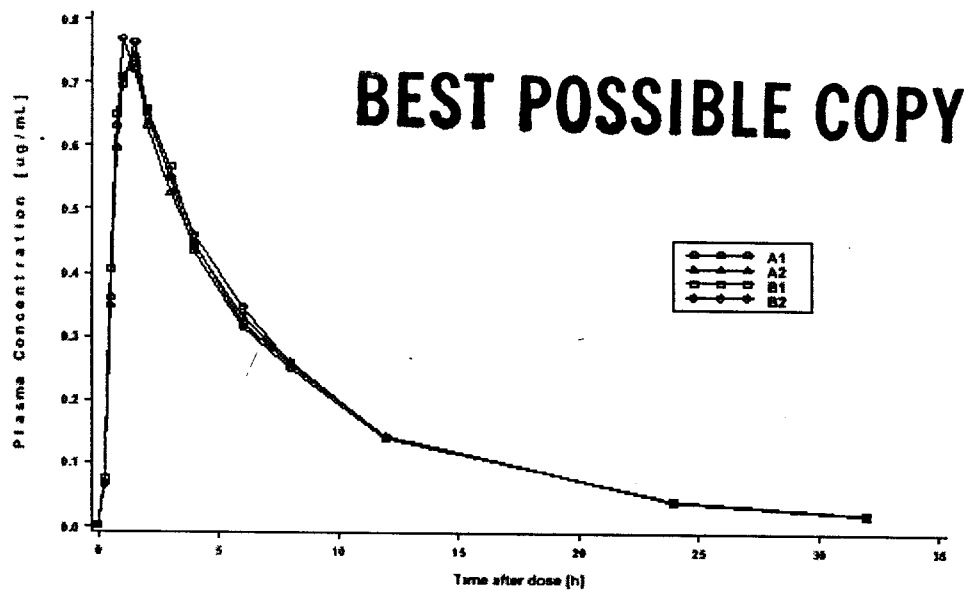

Figure 1. Plasma concentration-time profiles after administration of two batches of the commercial formulation of gemifloxacin (320 mg) with different dissolution profiles, given on separate dosing days. A1: First administration ———— release at 30 minutes, A2: Second administration ———— release at 30 minutes, B1: First administration - ———— release at 30 minutes, B2: Second administration - ———— release at 30 minutes.

Table.2. Pharmacokinetic parameters after administration of two batches of the commercial formulation of gemifloxacin (320 mg) with different dissolution profiles, given on separate dosing days. Batch A: >90% at 30 min, Batch B: 75% at 30 min.

	C_{max} (μg/mL)[a]	T_{max} (h)[b]	AUC (μg·h/mL)[a]	$T_{1/2}$ (h)[a]
Batch A (Dose 1) (n=22)	0.898±0.291 0.444-1.684	1.00 0.75-2.05	5.62±1.51 2.66-8.68	6.66±1.06 5.17-8.92
Batch A (Dose 2) (n=19)	0.847±0.220 0.473-1.219	1.50 0.73-2.98	5.64±1.48 3.36-8.67	6.46±1.06 4.88-8.51
Combined[c]	0.853±0.226 0.559-1.326	1.26 0.75-2.00	5.49±1.43 2.99-8.07	6.55±0.99 4.88-8.92
Batch B (Dose 1) (n=22)	0.905±0.245 0.459-1.363	1.03 0.75-3.10	5.70±1.47 3.15-8.28	6.51±0.95 5.29-8.64
Batch B (Dose 2) (n=19)	0.882±0.343 0.319-1.649	1.02 0.75-3.02	5.74±1.96 2.33-9.75	6.45±1.13 5.03-8.72
Combined	0.883±0.263 0.415-1.46	1.26 0.75-3.00	5.57±1.45 2.71-8.98	6.45±0.97 5.07-8.61
P.E.	1.02[d]	-0.06[e]	1.01[d]	
90% C.I.	(0.91, 1.15)	(-0.24, 0.19)	(0.91, 1.09)	

[a]: Mean±SD, range; [b]:Median, range; [c]:Average of geometric means of two doses; [d]: ratio of adjusted geometric means; [e]: median difference between formulations

Reviewer's comment: The results indicate that the difference in dissolution rate does not affect in vivo biovailability of gemifloxacin. In the original submission of this NDA, the sponsor proposed a dissolution specification of Q= ―― , (NLT ―― label claim released). The OCPB reviewer recommended to change this dissolution specification to Q= ―― (NLT ―― dissolution), based on the dissolution data that was provided by the sponsor. Since the results of this study demonstrated the bioequivalence of two batches of commercial formulation tablet of gemifloxacin with differing dissolution profiles, i.e., ―――――― dissolution at ~ min, the dissolution specification of Q= ―― 'NLT ―― dissolution), originally proposed by the sponsor, is considered to be acceptable.

Safety Results:

There were no deaths during this study. There was one serious adverse event (SAE) which resulted in hospitalization of the subject. However, the investigator also reported the lower abdominal pain as unlikely to be related to treatment with study medication. A total of 47 treatment-emergent adverse events were reported in 15 subjects. The most frequently reported AE was headache, followed by upper respiratory tract infection and nausea. All AEs were infrequent and gave no cause for clinical concern (with exception of the serious adverse event). Twenty one were considered not related, 16 were unlikely to be related, and 10 were suspected to be related to treatment.

Conclusions:

a. The commercial formulation of gemifloxacin 320 mg with a lower in-vitro dissolution profile (:~――release at 30 minutes) is bioequivalent (as evidenced by C_{max}

and AUC) to the commercial formulation of gemifloxacin with ——— release at ——— minutes.

b. Similar T_{max} indicated that the rate of absorption for gemifloxacin were similar for two formulations.

c. Based on the results of this study, the dissolution specification of Q=——→ (NLT ——— dissolution), originally proposed by the sponsor, is considered to be acceptable.

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8. · <u>Study 114:</u> **An open, randomized, three-way crossover study to investigate the tolerability and relative bioavailability of a pediatric suspension of gemifloxacin compared to the 320 mg tablet, and assess pharmacokinetic equivalence with respect to AUC of intravenous (250 mg) and tablet (320 mg) formulations of gemifloxacin in healthy adult volunteers**

NDA Vol. 6.018 – 6.020, pp 1-672

A new suspension formulation was developed for adults having difficulty in swallowing the tablet and for pediatric patients. This is the first study to give this suspension formulation to humans. On the other hand, data from different clinical studies showed similar systemic exposures after 250 mg intravenous (iv) and 320 mg oral administration. The objective of this study was tow-fold; (a) to investigate the absolute bioavailability of the pediatric suspension compared with that of the oral tablet and (b) to assess the pharmacokinetic equivalence between the 250 mg iv dose and 320 mg oral tablet after both doses was administered in the same subjects. The sponsor expected to use the 320 mg oral safety database in support of the iv formulation. The results showed that (a) the oral bioavailability of gemifloxacin from the pediatric suspension was ~25% lower than that from the oral tablet and (b) AUC_{0-inf} and C_{max} after the 250 mg iv dose was ~30% and ~50 %, respectively, higher compared with the 320 mg oral tablet.

Study date:
The first subject was screened on 28 March 2001. The first dose of study medication was administered on 18 April 2001 and the final dose was administered on 09 May 2001. The last study visit was on the 19 May 2001.

Objectives:
a) To investigate the relative bioavailability of a pediatric gemifloxacin suspension compared to the 320mg gemifloxacin tablet
b) To assess the pharmacokinetic equivalence in terms of AUC of 250 mg intravenous and 320 mg tablet formulations of gemifloxacin in healthy adult volunteers
c) To obtain tolerability data on the pediatric suspension.

Formulation:

Gemifloxacin tablet formulation: A white, film-coated, oval tablet contained 320mg (free base) gemifloxacin. Batch number: N00145.
Gemifloxacin intravenous formulation: Each 20 mL clear glass vial contained 250 mg gemifloxacin (free base) as a white to pale brown freeze-dried plug, which upon reconstitution with sterile water for injection, formed a clear, pale yellow to brown solution which must be further diluted prior to administration. Batch number: N99269.

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Study Design:

This study was an open-labeled, randomized, single dose, three-session crossover study in healthy male and female volunteers. Each volunteer participated in three sessions and was administered a single gemifloxacin dose of either tablet, intravenous or suspension formulations in each session. An interval of at least 5 days separated each of the three sessions. The following treatments were administered:

- 320mg gemifloxacin pediatric suspension administered orally in 10mL solution
- 320mg gemifloxacin tablet taken orally
- 250mg gemifloxacin intravenously infused over 1 hour

Blood samples for pharmacokinetic assay of gemifloxacin were performed at specified intervals throughout each study, until 48 hours post dose. Subjects rated the taste of the suspension formulation on a visual analogue scale.

Study Population and Demographic Data:

A total of 25 healthy male and female subjects were screened and entered this study. One subject did not receive the last dosing session. Demographic data of all subjects are shown in Table 1. All 24 dosed subjects were evaluable for both safety and pharmacokinetic analysis.

Table 1. Demographic data

Group	Parameter	Age (years)	Height (cm)	Weight (kg)	Race
Male	n	16	16	16	16 Caucasian
	Mean	38	179	83	
	SD	-	-	-	
	Range	20-60	164 - 195	64.0 - 101.1	
Female	n	8	8	8	7 Caucasian
	Mean	36	166	66.4	1 Other
	SD	-	-	-	
	Range	23-51	161 -175	56.8 – 72.0	
All Subjects	n	24	24	24	33% Female
	Mean	38	175	77.4	67% Male
	SD	10.3	10.0	12.6	96% Caucasian
	Range	20-60	161-195	56.8-101.1	4% Other

Safety Parameters:

Adverse event forms were completed pre-dose, 1, 12 and 48h post-dose on each dosing day and at follow-up, in addition to spontaneous reporting by the subject during the study. **Blood pressure, pulse and 12-Lead ECG measurements** were taken pre-study and at follow-up. **Hematology, clinical chemistry and urinalysis parameters** were assessed pre-study, pre-dose and 24h post-dose on each dosing day and at follow-up. A routine **urine drug screen** for undeclared drugs was performed on urine samples collected pre-study. Subjects provided a urine sample at pre-dose on all study days which was tested at random for undeclared drugs during the study. Urine **pregnancy**

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test was conducted in females at pre-study visit, pre-dose on each dosing day and at follow-up. Immediately after the oral suspension formulation of SB-265805, subjects were asked to rate the acceptability of the **suspension taste**.

Pharmacokinetic Parameters:
Blood samples (approximately 3 mL) were taken pre-dose and at 0.25, 0.5, 0.75, 1 (intravenous session: immediately prior to the end of infusion), 1.5, 2, 3, 4, 6, 8, 12, 24, 32 and 48 hour. During the intravenous session two additional samples were taken at 1.16 and 1.33 hour. Plasma samples were assayed for gemifloxacin using a method based on
————————— with ————— The samples were analyzed by ⊢—————
employing ————————————— with a lower limit of quantification of
————— using a 50 μL aliquot. The assay was linear with the range of ————
μg/mL. The within and between-run precisions were acceptable (————.

Non-compartmental analysis was used to calculate the pharmacokinetic parameters: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}), plasma clearance (CL), volume of distribution at steady state (Vd_{ss}) the apparent terminal half-life ($T_{1/2}$), and the absolute bioavailability following an oral dose (F).

Statistical Methods: /
Log-transformed AUC and C_{max} of gemifloxacin were analyzed by ANOVA fitting terms for sequence, subject(sequence), period and regimen. Point estimates and 90% confidence intervals for the differences "Suspension − Tablet" ("A:B") and "Intravenous −Tablet" ("C:B") were constructed.

Pharmacokinetic Results:
Plasma concentration time-profiles of gemifloxacin and the relevant pharmacokinetic parameters of gemifloxacin after single administration of pediatric suspension, tablet formulation and intravenous formulation are shown in Figure 1 and Table 2, respectively. The mean plasma concentration-time profiles showed that the pediatric suspension had lower systemic availability than the tablet formulation of the same dose. For both formulations, the individual maximum plasma gemifloxacin concentration was observed between 0.5 and 2 hours after administration. The mean plasma drug concentrations after a single 1 hour intravenous infusion of 250 mg were higher compared with after oral administration of pediatric suspension and tablet formulation of 320 mg. The terminal half-lives of gemifloxacin were independent of formulation and dose route.

Comparisons of AUC_{0-inf} and C_{max} between the formulations from ANOVA are presented in Table 3. AUC_{0-inf} and C_{max} for the pediatric suspension were on average, 22% and 25% lower, respectively, compared with oral tablet formulation. On the other hand, AUC_{0-inf} and C_{max} for intravenous formulation were on average, 29% and 53% higher than the adult oral tablet, respectively. The 90% confidence interval for AUC_{0-inf} and C_{max} did not completely fall within the range 0.80-1.25 and, hence, the equivalence criteria have not been met.
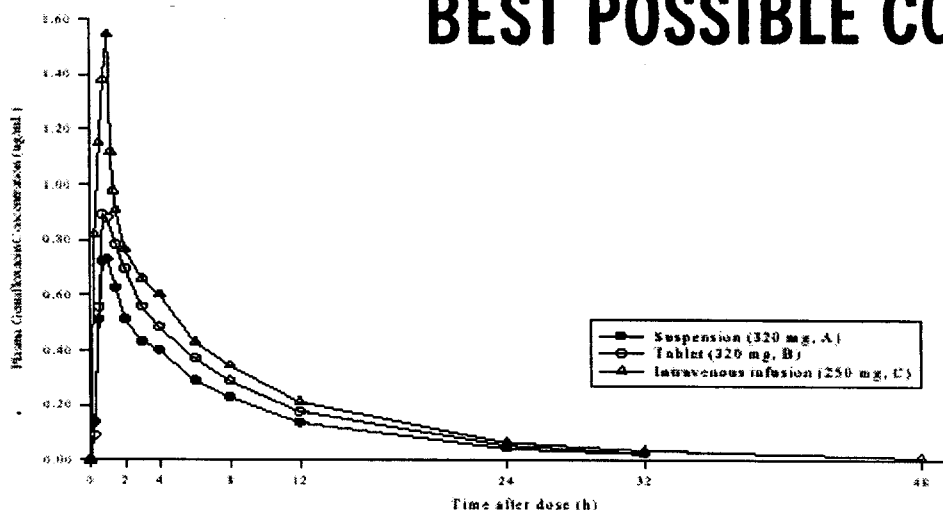
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Figure 1. Mean plasma gemifloxacin concentration (μg/ mL) versus time profiles following doses of 320 mg gemifloxacin as a pediatric suspension and tablet, and following a single 250 mg gemifloxacin intravenous infusion (1 hour) to healthy adult volunteers.

Table 2. Pharmacokinetic parameters of gemifloxacin after single administration of pediatric suspension 320 mg, tablet formulation 320 mg and intravenous formulation 250 mg.

	Suspension (320 mg)	Tablet (320 mg)	I.v. (250 mg)
AUC_{0-inf} $(\mu g \cdot h/mL)^a$	5.38±1.68 2.76-9.25	6.78±2.06 3.77-13.13	8.60±1.90 5.94-13.81
C_{max} $(\mu g/mL)^a$	0.755±0.204 0.453-1.11	1.03±0.24 0.483-1.587	1.57±0.34 0.893-2.123
T_{max} $(h)^b$	1.00 0.52-1.50	1.00 0.52-2.02	1.00 0.75-1.08
$T_{1/2}$ $(h)^a$	7.58±1.66 5.44-13.1 —	8.21±2.26 5.32-13.3	8.33±2.16 5.13-12.0
CL $(L/h)^a$			30.3±6.0 18.1-42.1
V_{ss} $(L/kg)^a$			3.52±0.56 2.49-4.41
F $(\%)^a$	48.5±10.1	61.3±10.1	

[a]: Mean±SD, range; [b]: median, range

Table 3. Comparisons of gemifloxacin pharmacokinetics between formulations

Parameter	N	Comparison	Point Estimate	(90% C.I.)
Primary				
AUC(0-inf) (ug.h/mL)	23	Suspension:Tablet	0.78	(0.73, 0.85)
Cmax (ug/mL)	23	Suspension:Tablet	0.75	(0.67, 0.83)
AUC(0-inf) (ug.h/mL)	23	Intravenous:Tablet	1.29	(1.20, 1.39)
Secondary				
Cmax (ug/mL)	23	Intravenous:Tablet	1.53	(1.38, 1.70)

Reviewer's comment:
Unlike the sponsor's intention to use safety database of 320 mg oral tablet in support of the intravenous formulation, the pharmacokinetics of the 250 mg intravenous dose was not equivalent with that of the 320 mg oral tablet. Based on the bioavailability of the oral tablet in the present study, i.e., 60%, an intravenous dose of 200 mg (0.6*320 mg=192mg) is recommended to be tested if the sponsor plans to further develop the intravenous formulation of gemifloxacin using the safety database of oral tablet.

SAFETY RESULTS:
A total of 21 subjects experienced 58 adverse events (AEs) of which 53 were treatment-emergent AEs (TEAEs) during this study. Most of TEAEs were mild (37 AEs) or moderate (16 AEs). Ten AEs were considered by the Investigator not related, 18 AEs unlikely and 25 AEs were of probable relationship to gemifloxacin. The 25 probable relationship AEs were pain [in the iv infusion arm] (15), taste perversion [reported in the suspension session] (4), abnormal vision (1), diarrhea (2), flatulence(1), headache (1), paresthesia [in the infusion arm] (1).

Reviewer's comment:
The pain in the iv infusion arm, as an AE, should be evaluated with placebo control. This study did not have a placebo control group. Therefore, it is not clear if the pain is related to the gemifloxacin or an iv infusion.

Conclusions:

1. The absolute bioavailability of gemifloxacin from the pediatric suspension (320 mg) was lower than that of the 320 mg tablet, i.e., F = ·—, for the suspension; —— for the tablet vs. the 250 mg IV dose.

2. In terms of AUC_{0-inf} (8.60 vs 6.78 $\mu g \cdot h/ml$) and C_{max} (1.57 vs 1.03 $\mu g/ml$), the 250 mg intravenous dose was not equivalent with the 320 mg oral tablet.

3. The intravenous administration of gemifloxacin (250mg) was associated with mild or moderate pain in the infusion arm during and post infusion in the majority of subjects (16 of 24). Gemifloxacin 320mg suspension formulation was variable in the acceptability of its taste, and left a bitter aftertaste in some subjects (4 of 24).

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NDA 21-158

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

|	
NDA:	21-158
Submission Date:	December 15, 1999
Drug Product:	Gemifloxacin Mesylate 400 mg Tablets
Trade Name:	FACTIVE®
Sponsor:	SmithKline Beecham Philadelphia, PA
Submission Type:	NDA for an NME (Fluoroquinolone Antibiotic)
Review Category:	1S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.

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I. INTRODUCTION / BACKGROUND

Gemifloxacin (SB265805) is a synthetic fluoroquinolone antibacterial agent, originally synthesized by LG Chemical Ltd. (Taejon, Korea) and currently under development by SmithKline Beecham Pharmaceuticals. Like the other fluoroquinolones and quinolones in this class, the mechanism of bactericidal activity of gemifloxacin is primarily via inhibition of bacterial DNA gyrase.

Gemifloxacin contains a nitrogen rather than carbon at the 8-position of its chemical structure, and thus, is one of a new class of quinolones called fluorinated naphthyridones (**see structure below**). This structural modification, among other modifications, purportedly results in greater *in vitro* activity/potency against Gram-positive organisms (e.g., *Streptococci, Staphylococci*), while still retaining good Gram-negative activity that is characteristic of all members of this class.

Gemifloxacin Mesylate Structural Formula:
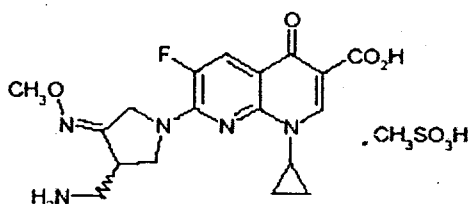
Gemifloxacin contains one chiral carbon and is being developed as a racemic mixture of the (+) and (−) enantiomers. The sponsor demonstrated that both enantiomers have approximately the same antimicrobial activity *in vitro*. The proposed commercial formulation is an immediate release film coated tablet containing 400 mg gemifloxacin mesylate. The molecular weight of the pure free base of gemifloxacin is approximately 80% that of the mesylate salt, thus 400 mg mesylate = 320 mg pure free base. The proposed clinical dosage regimen for the tablet is 400 mg QD of varying duration, depending on the infection (**see below**). Dosage adjustment will be needed for patients with renal impairment (**see below**).

Gemifloxacin is currently not approved in any country. However, worldwide marketing applications are currently being prepared for the proposed use of gemifloxacin for the treatment

1

of community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute bacterial sinusitis, uncomplicated urinary tract infections and pyelonephritis/complicated urinary tract infections.

II.   PROPOSED INDICATIONS / DOSAGE AND ADMINISTRATION

The proposed labeling for gemifloxacin is provided with this review as **Appendix 1**. The indications and dosage and administration sections, as originally proposed in the labeling, are as follows:

INDICATIONS:
Acute Bacterial Exacerbation of Chronic Bronchitis caused by *Streptococcus pneumoniae,* including penicillin and macrolide-resistant strains; *Haemophilus influenzae* including β-lactamase-producing strains; *Haemophilus parainfluenzae; Moraxella catarrhalis; Staphylococcus aureus.*

[   ]

Community-Acquired Pneumonia caused by *Streptococcus pneumoniae* including penicillin and macrolide-resistant strains; *Haemophilus influenzae* including β-lactamase-producing strains; *Moraxella catarrhalis; Mycoplasma pneumoniae; Chlamydia pneumoniae; Legionella pneumophila; Staphylococcus aureus; Coxiella burnetti.*

[   ]

DOSAGE AND ADMINISTRATION:

INDICATION	DOSE	DURATION
Acute Bacterial Exacerbation of Chronic Bronchitis	One 320 mg tablet daily	5 days
Community-Acquired Pneumonia	One 320 mg tablet daily	7 days

*Therapy may be extended to ⎯⎯ of therapy in cases of ⎯⎯⎯⎯

Renally Impaired Patients: Dose adjustment in patients with mild/moderate renal impairment is not required. Some modification of dosage is recommended for patients with severe renal dysfunction.

2

The following table provides dosage guidelines for use in patients with renal impairment:

**Recommended Starting And Maintenance Doses
For Patients With Impaired Renal Function**

Creatinine Clearance (mL/min)	Dose
≥40	See Usual Dosage
<40	160 mg q24h

Patients on hemodialysis therapy should receive 160 mg q24h.

Use in the Elderly or Hepatically Impaired Patients: No dosage adjustment is recommended.

III.   **SUMMARY OF HUMAN PHARMACOKINETICS (PK) AND BIOAVAILABILITY (BA)**

The following is a brief summary of the most relevant Clinical Pharmacology and Biopharmaceutics issues that arose from the review of **Item 6** of the NDA, as well as other pertinent sections of the NDA. More detailed reviews of this information can be found in **APPENDIX 2: REVIEW OF HUMAN PHARMACOKINETICS AND BIOPHARMACEUTICS STUDIES FROM ITEM 6 and APPENDIX 3: GEMIFLOXACIN TABLET – FORMULATION INFORMATION AND IN VITRO DISSOLUTION,** which are available upon request from either the OCPB Reviewer, the OCPB Division of Pharmaceutical Evaluation 3 (DPE 3, HFD-880), or the Project Manager from the Division of Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590).

A top-level summary of the PK of gemifloxacin, as obtained across the various PK studies after repeat oral dosing with 320 mg QD, is provided in the following table. In general, the PK of gemifloxacin was adequately characterized in healthy subjects and patients with infection.

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PK Assessments in Healthy Subjects	PK Parameters After 320 mg Q24 hr (Unless Noted) Expressed as Mean ± SD (Range)
Absorption and Systemic Bioavailability	Tablet Absolute Bioavailability 71% (95% CI 60-84%) $AUC(0-24)_{ss}$ 9.9 ± 3.1 (4.7 – 20) µg•hr/mL $Cmax_{ss}$ 1.6 ± 0.51 (0.7 – 2.6) µg/mL Tmax 1.0 (0.5 – 4.0)
Food Effects	None
Distribution	Moderate Protein Binding: 60% – 70% Bound Penetration into Nasal Secretions, Lung Tissues / Lung Fluids >> Plasma
Metabolism	Minimal Hepatic CYP450 Metabolism Excreted Mostly Unchanged Minor Metabolic Routes (≤10-12%): Glucuronidation, N-Acetylation, Geometric Isomerization
Excretion	Dual Routes: Urine and Feces Urine: 30-40% Unchanged Gemifloxacin Feces: 60% Unchanged Gemifloxacin + Metabolites; ~40% Unchanged Gemifloxacin

Elimination Kinetics	T1/2: 7 ± 2 (4 – 12) hrs
	
	CL/F: 36 ± 12 (16 – 68) L/hr
	    [600 ± 200 (267 – 1133) mL/min]
	
	CLr: 12 ± 4 (5 – 18) L/hr
	    [200 ± 67 (83 – 300) mL/min]

Disposition Kinetics	Dose Proportional Increases in AUC and Cmax after Single Doses from 40 to 640 mg Minimal Plasma Accumulation at Steady State (≤15% at 320 mg QD) Linear and Predictable PK from Single to Repeat Dosing
Significant Interactions with Other CYP450 Drug Substrates Other Significant Drug Interactions	None for Theophylline, Warfarin, Omeprazole, Oral Contraceptives, (Digoxin) Antacids, Sucralfate, Ferrous Sulfate All Significantly Decrease Oral Bioavailability Probenecid Significantly Increases Exposure (AUC)
Dosage Adjustment Needed for: Renal Impairment Hepatic Impairment	 Yes; 160 mg Q24 hr at CLcr <50 mL/min, Including Hemodialysis and CAPD No Adjustment for Mild (Class A) to Moderate (Class B) Impairment; Not Adequately Studied in Severe Impairment (Class C)
Effects of Age on PK Effects of Gender on PK Effects of Body Weight on PK	None None None

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A. CLINICAL PHARMACOLOGY ISSUES

1. Dosage Regimen

a) Was a rationale for the proposed 320 mg QD oral dosage regimen for gemifloxacin provided in the NDA?

Several *in vitro* and *in vivo* microbiological experiments were performed to assess the adequacy of the 320 mg Q24 hr dosage regimen. The *in vitro* evaluations involved using established models for infection and simulation of gemifloxacin concentrations and/or Cmax and AUC values that would be achieved following the 320 mg Q24 hr oral dose to humans. These models indicated that the concentrations and/or exposure to gemifloxacin achieved with 320 mg Q 24 hr would adequately exceed the MIC's of the pathogens that were typically observed in the clinical trials. *In vivo* animal models of various infections also demonstrated adequate protection at doses equivalent to the 320 mg Q24 hr regimen. There were also 2 Phase II dose-ranging efficacy and safety studies of gemifloxacin that suggested adequacy of the 320 mg Q24 hr regimen over lower gemifloxacin doses in the treatment of bacterial infections. In **Study 001**, oral gemifloxacin doses of 80 mg Q24 hr, 160 mg Q24 hr, and 320 mg Q24 hr were compared to a another quinolone for the treatment of acute exacerbation of chronic bronchitis (AECB). The clinical efficacy results showed that the 80 mg, 160 mg, and 320 mg dose regimens were equally effective as the comparator. However, bacteriological efficacy was significantly reduced for the 80 mg and the 160 mg dose regimens compared to the 320 mg regimen. In **Study 002**, 160 mg Q24 hr and 320 mg Q 24 hr gemifloxacin regimens were compared against a quinolone comparator for the treatment of uncomplicated skin and skin structure infections. The clinical efficacy results showed the 160 mg and 320 mg gemifloxacin regimens to be equally effective, although the clinical success rate was slightly lower for the 160 mg regimen. Both gemifloxacin regimens appeared to be equally effective to the comparator, but these results were inconclusive due to the study being under powered.

The results from these microbiology and clinical studies, together with those of the *in vitro* susceptibility tests (i.e., MIC determinations) and knowledge of the PK in humans resulted in the sponsor deciding to use only the 320 mg Q24 hr oral dose regimen in the Phase III clinical efficacy and safety trials of respiratory and urinary tract infections.

b) Was any PK/PD evaluation performed with the clinical dose of 320 mg Q24 hr to evaluate the relationship with either clinical efficacy or safety of this proposed regimen?

A Population PK/PD analysis was performed to explore the relationships between derived PK parameters of exposure (i.e., AUC), bacterial susceptibility (i.e., MIC) and efficacy outcome measures in patients with respiratory infections. **The Pop PK/PD analysis and study report (RSD-100XPZ/2) and was formally reviewed by the DPE 3 Pharmacometrics Reviewer (D. Wang, Ph.D.). The Pharmacometrics Review is included in Appendix 2.**

For this analysis, population PK estimates of AUC were determined from 4 Phase III clinical efficacy and safety trials of gemifloxacin at the 320 mg Q24 hr dosage regimen. Respiratory infections that were treated in these protocols included community acquired pneumonia, and acute exacerbation of chronic bronchitis. Individual MIC data were tabulated along with the post-hoc estimates of AUC (determined from the Pop PK analysis) for each of 451 patients and the AUC/MIC ratios calculated. The highest MIC of the pathogen on Day 1 of therapy was used to calculate the AUC/MIC ratios. The AUC data and AUC/MIC ratios were combined from all 4 studies and used to explore any relationships with clinical and/or bacteriological outcomes (i.e., success or failure).

Overall, the AUC and MIC data for all 451 patients showed a wide range of values, and thus, so did the AUC/MIC ratios. This data is shown in the table below.

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Summarized PK and PK/PD Parameters Across All Patients in Four Phase III Respiratory Infection Studies (009, 049, 061, and 068)			
	AUC (µg•hr/mL)	MIC (µg/mL)	AUC/MIC Ratio
N	451	451	451
Minimum	3.33	0.001	0.794
Maximum	42.7	8.000	22922
Median	9.19	0.092	1430
Mean	8.27	0.015	658
SD	4.52	0.585	2367

The AUC averaged ~8 to 9 µg•hr/mL, which was similar to that determined in the healthy subjects from the repeat dose PK studies. However, the range of AUC values in these patents (i.e., ~3 to 43 µg•hr/mL) was wider than that observed in the healthy volunteer PK studies. The mean and median AUC/MIC ratios were high and the individual ratio values varied widely from ~0.8 to ~23000. Approximately 90% of the 451 patients had AUC/MIC ratios of at least 80 and greater (i.e., ~406 patients) and only 12 patients had ratios below 50. The overall clinical and bacteriologic success rates across the 4 studies were also quite high at over 90%. Because of the limited number of failures in these studies, no clear relationship could be derived between AUC/MIC and the probability of successful or unsuccessful outcomes. Only a slight trend was observed for a lower proportion of patients with successful clinical and/or bacteriological outcomes having AUC/MIC ratios <50. These results with gemifloxacin are not inconsistent with those that have been reported for other fluoroquinolones. Although not particularly compelling, the results do suggest that the 320 mg Q24 hr regimen would be adequate to treat respiratory infections. A major shortcoming to this analysis is not having any PK/PD data from lower doses of gemifloxacin, which may have allowed for analysis of a greater number of clinical and/cr bacteriologic failures.

No evaluation of gemifloxacin exposure (i.e., AUC) and the potential relationship to safety was performed in this analysis.

2. PK Assessment in Patients with Infection

a). How does the systemic exposure/PK of gemifloxacin in patients with infection compare to that in healthy volunteers? Are there any patient characteristics/covariates that significantly effect the PK of gemifloxacin?

To address these questions, a population PK (Pop PK) analysis was performed. **The Pop PK analysis and study report (RSD-100XPX/2) and was formally reviewed by the DPE 3 Pharmacometrics Reviewer (D. Wang, Ph.D.). The Pharmacometrics Review is included in Appendix 2.**

The goals of this analysis were to (1) characterize the PK of gemifloxacin after repeated oral administration of 320 mg QD in patients from Phase III clinical trials of infection, (2) evaluate the influence of various covariates, such as patient demographics, smoking status, and renal function, on gemifloxacin disposition, and (3) investigate the relationship between predicted gemifloxacin exposure (AUC) and the occurrence of selected adverse events.

Gemifloxacin plasma concentration-time data were obtained from 5 Phase III clinical efficacy and safety trials (Studies 009, 013, 049, 061 & 068) of repeat oral gemifloxacin administration of 320 mg QD to patients with respiratory and urinary tract infections. The duration of drug therapy in these studies ranged from 5 to 10 days. A sparse PK sampling design was implemented in these studies for the purpose of conducting the population PK analysis. The majority of patients had 2

blood samples collected over the duration of their drug therapy: one sample immediately prior to and the other at 0.5 – 12 hours after the morning dose.

Gemifloxacin plasma concentrations from 1423 patients were included in the Pop PK analysis. Eighty percent (N=1138) of these patients were randomly selected and included in model building. The remaining 20% of patient data were used for model validation. The patient demographic data are summarized in the table below.

Demographic Factor	Mean	Range
Age (yr.)	54	16 - 92
Weight (kg)	72	29 - 166
Creatinine Clearance* (mL/min)	97.4	12.8 - 150
Gender		Men = 745, Women = 677
Race		Caucasians = 988, Blacks = 46, Oriental = 165, Hispanics = 119 & of Other Ethnic Origin = 103, Unknown = 2
Smoking Status		Smokers = 388, Non Smokers = 1034
*Calculated based the equation of Cockcroft and Gault; Values >150 mL/min (N=170) were set to 150 mL/min		

Note that a wide range of renal function was evaluated from CLcr ~13 to 150 mL/min.

Plasma gemifloxacin concentration-time data were analyzed using Nonlinear Mixed Effect Mcdeiing as implemented in the computer program NONMEM (Version V). A two-compartment model with first-order absorption and elimination from the central compartment was used as the structural model. The model was parameterized in terms of oral clearance (CL/F), apparent central (V2/F) and peripheral distribution volume (V3/F), distributional clearance (Q) and absorption rate constant (Ka).

For the model building dataset, various covariates (fixed effects) were assessed for their ability to account for some of the inter-individual variability observed in CL/F and V2/F. The covariates examined included the influence of various patient demographic (e.g., age, weight, gender, race and smoking status) and physiological (creatinine clearance (CrCL)) variables and the presence of co-existing diseases (hypertension, heart failure, asthma, respiratory disorder, biliary disorder, kidney disorder and diabetes mellitus). All covariates were examined for potential effect by graphical assessments and by the addition of each of the covariates individually on CL/F and V2/F in the model and then in combination. In addition, the relationship between the individual post-hoc (Bayesian) estimates of gemifloxacin CL/F in patients on selected concomitantly administered drugs (diuretics, calcium, estrogens, estradiol and progesterones) versus those who were not on any other medications were graphically investigated. Following establishment of the final model, Bayesian estimates of steady-state gemifloxacin AUC values for all patients across the 5 studies were compared between patients reporting selected adverse events with those who did not report any adverse events.

The Pharmacometrics Reviewer found the Pop PK approach of the sponsor to be adequate.

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7

The results showed that the PK parameters derived from the final population model were similar to those obtained from the PK studies in healthy volunteers (see table below).

Final Population PK Parameters from 1423 Patients in Phase III Efficacy and Safety Trials

	Population Estimate (Range)	Precision of Estimate & Between Patient Variability	95% C.I.
CL/F (L/hr)	38.1 (17.3 – 51.2)	1.5% 40%	(38.0, 40.4)
Vd/F (L)	281 (164 – 522)	2.2% 68%	(268, 291)
T1/2 (hr)	~7	NA	NA
AUC(0-24) (μg•hr/mL)	9.3 (3.3 – 48.5)	NA	NA

Note the wide range of estimates for CL/F and Vd/F, as reflected in the ranges and the large inter-individual variability estimated for both of these parameters.

The final population model indicated that creatinine clearance (CLcr) and body weight (WT) were the only significant covariates affecting the PK of gemifloxacin. Gemifloxacin oral clearance (CL/F) was shown to decrease in a linear fashion with the decrease in CLcr. This may be expected since ~30-40% of gemifloxacin is excreted as unchanged drug in the urine. The apparent volume of distribution (Vd/F) was also shown to increase in a linear fashion with the increase in body weight.

The final population model related CL/F to CLcr through the following equation:
CL/F (L/hr) = 38.1 + (CLcr – 97) x 0.25

Thus, at the median CLcr observed in this patient population (97 mL/min), the predicted gemifloxacin CL/F was 38.1 L/hr. This relationship also predicted that CL/F changes by ~2.5 L/hr for every 10 mL/min change in CLcr.

The final population model also related body weight (WT) to gemifloxacin apparent volume of distribution (Vd/F) by the following equation:
Vd/F (L) = 281 + (WT – 70) x 2.83

Thus, at the population median body weight of 70 kg, the predicted apparent volume of distribution was 281 L (4 L/kg). This relationship also predicted that Vd/F changes by ~28 L for every 10 kg change in body weight.

In summary, dosage adjustment will be needed based on renal function (i.e., CLcr) but not on body weight. No other covariates tested were found to significantly affect the PK of gemifloxacin, i.e., age, gender, race, and smoking. In addition, no other co-existing disease or concomitantly administered medications (i.e., diuretics, **calcium**, estradiol/ethinylestradiol, estrogen or progesterone) examined were found to significantly influence gemifloxacin disposition.

The potential relationship between the population estimates of AUC(0-24) and selected adverse events (AE) was explored by comparing box plots of AUC for those patients without AE's and the AUC for those patients with the selected AE. The AE's selected were headache, nausea, vomiting, abdominal pain, rash, hyperglycemia, diarrhea and elevated hepatic enzymes. These AE's represented the more common ones reported in the Clinical Trials and in the PK studies of healthy subjects.

The results demonstrated that the medians and ranges of the gemifloxacin AUC(0-24h) values between patients reporting these AE's were similar to those for patients who did not experience AE's. Thus, these selected adverse events did not appear to be related to systemic gemifloxacin exposure.

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3. Dosage Adjustment in Renal or Hepatic Failure

a). Is dosage adjustment needed in patients with renal impairment?

The sponsor proposed a reduction in the gemifloxacin dosage to 160 mg Q24 hr for patients with CLcr <40 mL/min. The OCPB reviewer proposes a slightly different recommendation that the dose be reduced at ···

This issue was addressed through a Clinical Pharmacology study in subjects with varying degrees of renal impairment (**Study 031**) and through the Pop PK analysis which evaluated the relationship between gemifloxacin CL/F and CLcr.

Clinical Pharmacology Study 031 evaluated the effects of renal impairment on the PK and safety of gemifloxacin after a single oral dose of 160 mg to 6 parallel groups of male and female subjects with varying degrees of renal function:
1) **Normal function: mean (range) CLcr 115 (69-144) mL/min (N=8);**
2) **Mild impairment: mean (range) CLcr 77.8 (71.0-85.0) mL/min (N=5);**
3) **Moderate impairment: mean (range) CLcr 47.3 (36.0-61.0) mL/min (N=6);**
4) **Severe impairment: mean (range) CLcr 16.1 (9.0-23.0) mL/min (N=7);**
5) **Hemodialysis (N=6);**
6) **Continuous Ambulatory Peritoneal Dialysis (CAPD; N=6)**

The results showed that although Cmax was not affected by renal impairment, systemic exposure to gemifloxacin, i.e., AUC(0-inf), increased as creatinine clearance decreased. The mean AUC(0-inf) values were substantially increased in the moderate and severely impaired subjects by 85% and 74%, respectively, relative to volunteers with normal renal function. In the subjects on hemodialysis and CAPD, the mean AUC(0-inf) values were 2.1- and 2.4-times, respectively, that of the healthy group. **The increases in AUC(0-inf) were found to be statistically significant for the moderate, severe, and both dialysis groups when compared to the normal renal function group. No statistically significant differences in AUC(0-inf) were detected for the mild renal impairment group, nor for Cmax for any of the renal impairment groups. The increases in AUC(0-inf) for the moderate, severe, and dialysis subjects would be considered pharmacokinetically significant, and may also potentially be clinically significant.**

Both total gemifloxacin clearance (CL/F) and renal clearance (CLr) appeared to be linearly related to creatinine clearance. Mean CL/F values were reduced in the moderate and severe renal impairment subjects by 46%, and 42%, respectively. In both the hemodialysis and CAPD subjects, CL/F was reduced on average by 52% and 58%, respectively. The reductions in CLr were more substantial, with decreases of 73%, and 87% in the moderate and severe renal impairment groups, respectively. As a result of the decrease in gemifloxacin clearance, half-life was substantially increased with renal impairment. The mean T½ estimates were at least doubled in all renal impairment groups, including the mild renal impairment and both dialysis groups. **Statistically significant decreases in CL/F, CLr, and T½ were detected for the moderate and severe renal impairment groups, and for both dialysis groups (where applicable), as compared to the normal renal function group. The reductions in CL/F and CLr, and the prolongation of T½ in the moderate, severe and both dialysis groups would be considered pharmacokinetically significant, and may also potentially be clinically significant.**

Overall, the results from Clinical Pharmacology Study 031 indicated that dosage adjustment is needed for the moderate impairment, severe impairment, and dialysis subjects. Since gemifloxacin AUC values were increased to nearly twice and CL values reduced by at least one-half starting from the moderate impairment group, the dosage

The **Population PK** analysis showed similar findings to the **Clinical Pharmacology Study 031.**
The relationships between the estimates of AUC(0-24) and CLcr and between gemifloxacin CL/F
and CLcr from the Pop PK analysis are shown in the figures below.

**Relationship Between Model Predicted (Solid Line) and Individual Bayesian Estimates of
Gemifloxacin AUC(0-24) and Creatinine Clearance Following Repeated Doses of 320 mg
Q24 hr**
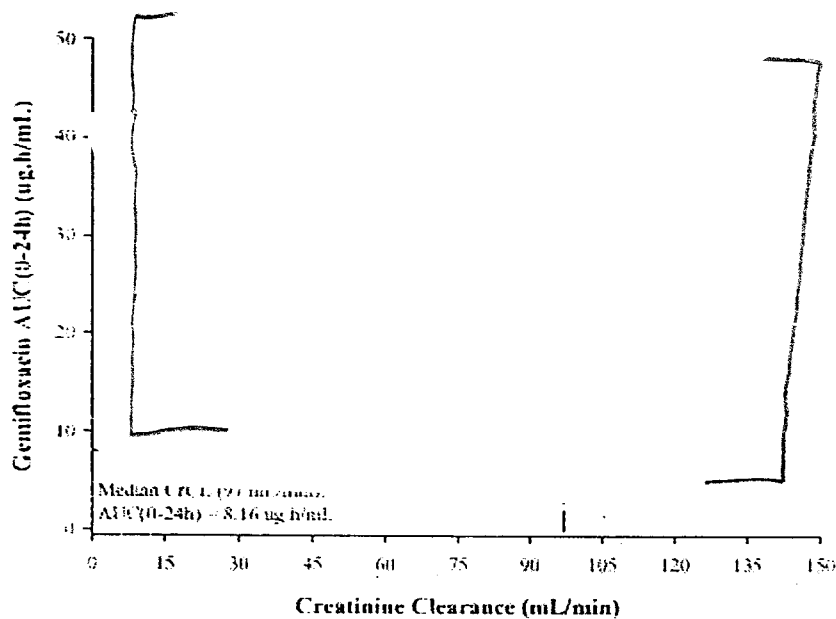
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Relationship Between Model Predicted (Solid Line) and Individual Bayesian Estimates of Gemifloxacin CL/F and Creatinine Clearance Following Repeated Doses of 320 mg Q24 hr
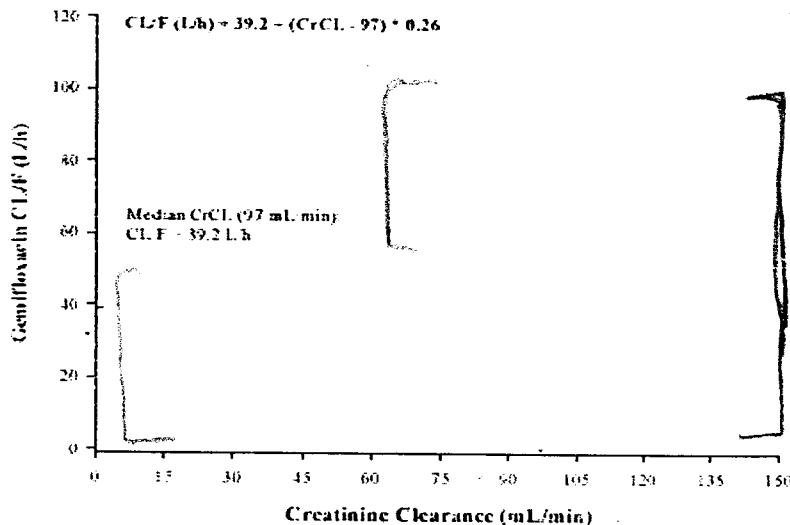
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From these plots, it can be seen that although gemifloxacin CL/F and CLcr appear to be linearly related. systemic exposure to gemifloxacin (i.e., AUC) and CLcr are not linearly related. At CLcr values at approximately <60 mL/min, a larger number of AUC(0-24) estimates for gemifloxacin start to exceed those values determined in the majority of those patients with CLcr greater than approximately 80 mL/min. Note also, that there is a great deal of overlap of AUC(0-24) estimates for patients with renal impairment and those with CLcr values above 80 mL/min. Although there was no relationship between AUC(0-24) and the incidence of some selected AE's in the Pop PK analysis **(see previous Question 2)**, it would be reasonable to adjust the dose in those patients with excessive AUC estimates (i.e., those with lower CLcr values) to avoid unnecessary systemic exposure.

In the sponsor's analysis of these relationships, it was noted that following repeat doses of 320 mg Q24 hr to a patient with CLcr of 40 mL/min, the predicted AUC(0-24) estimate would only increase 1.4-times that of a patient with "normal" renal function at CLcr 80 mL/min (i.e., AUC(0-24) ~13 μg•hr/mL at 40 mL/min vs. ~9.2 μg•hr/mL at 80 mL/min). Although the values determined by the sponsor are correct, a more appropriate comparison would be between the patient with CLcr at 40 mL/min and a patient with "normal" renal function at CLcr 110 mL/min. This would be more consistent with the median CLcr of 97 mL/min observed in the Pop PK analysis. In the latter comparison, the Pop PK relationship between CL/F and CLcr predicts that AUC(0-24) in the patient with CLcr of 40 mL/min would be increased 1.7-times that of the patient with CLcr of 110 mL/min (i.e., AUC(0-24) ~13 μg•hr/mL at 40 mL/min vs. ~7.5 μg•hr/mL at 110 mL/min). This latter comparison was more consistent with the results of the **Clinical Pharmacology Study 031** that showed mean AUC was increased ~75% in the moderate impairment group (mean CLcr 47 mL/min). Similarly, the predicted AUC(0-24) estimate in a patient with CLcr of 50 mL/min would be increased ~1.6-times that of the patient with CLcr of 110 mL/min.

Additional analysis of the Pop PK data by the DPE 3 Pharmacometrics Reviewer (D. Wang, Ph.D.) revealed that reduction of the gemifloxacin dose to 160 mg Q24 hr for the patients with

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11

CLcr <50 mL/min resulted in a more even distribution of the predicted AUC(0-24) estimates across the entire patient population that was studied, as compared to when dose reduction was at CLcr <40 mL/min. **Thus, based on these additional results the OCPB reviewer recommends that the gemifloxacin dose be reduced to** _____ **instead of the sponsor's proposed recommendation at** _____

b). Is dosage adjustment needed in patients with hepatic impairment?

The sponsor proposed no dosage adjustment in patients with mild to moderate hepatic impairment, and also indicated that although the data was limited, no difference in the PK of gemifloxacin was observed in patients with severe hepatic impairment (i.e., N=3). The OCPB reviewer agrees with the sponsor's proposed recommendation that no dosage adjustment is needed in mild to moderate hepatic impairment. However, a greater number

(see also VII. Potential Phase 4 Studies).

Clinical Pharmacology Study 032 evaluated the effects of hepatic impairment on the PK and safety of gemifloxacin. A single oral dose of 320 mg was administered to healthy subjects (N=3) and subjects with mild (Class A, N=9), moderate (Class B, N=11), and severe (Class C, N=3) hepatic impairment. The sponsor prematurely terminated the study to allow new toxicology findings with gemifloxacin to be fully evaluated. Thus, the planned number of 10 subjects per group was not reached in the severe hepatic impairment group or in the healthy group. For the healthy group, PK data from 3 previous PK studies of single dose gemifloxacin 320 mg were used to produce a total number of 45 healthy subjects as the historical control group. Formal statistical analyses were performed using this control group and only the mild and moderate hepatic impairment groups. No statistical evaluation was conducted with the severe hepatic impairment group. *This approach was acceptable to the OCPB reviewer.*

The results showed that, on average, mild and moderate hepatic impairment had a moderate effect on the overall systemic exposure to gemifloxacin. The point estimates for mean AUC(0-inf) indicated that subjects with mild and moderate hepatic impairment had increases of 30% and 34%, respectively, as compared to the healthy volunteers. The increases in Cmax for the mild and moderate hepatic impairment groups were, on average, 25% and 19%, respectively. **Because gemifloxacin demonstrates linear PK with little or no accumulation in healthy subjects after repeated dosing with 320 mg, these average increases in AUC and Cmax of ~30% or less in mild and moderate hepatic impairment subjects would not be expected to be pharmacokinetically significant. Note, however, since this present study did not evaluate the PK of gemifloxacin following multiple doses, the extent of drug accumulation in hepatically impaired patients is not definitively known. The reductions in gemifloxacin clearance of ~15 to 40% and the increase in T½ of ~1 to 2 hours for the mild and moderate hepatic impairment subjects would also not be cause for concern from a pharmacokinetic perspective.**

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4. Drug-Drug Interactions

a). Are there any significant PK drug interactions with gemifloxacin?

There were no significant metabolism-based (i.e., hepatic CYP450 enzymes) PK interactions with gemifloxacin. A lack of an interaction potential was demonstrated through *in vitro* inhibition studies with human hepatic microsomal preparations for the major CYP450 enzymes, i.e., CYP1A2, CYPCYP2C9, CYP2C19, CYPP2D6, CYP2E1, and CYP3A4. This lack of interaction was also corroborated *in vivo* through clinical pharmacology studies that demonstrated no PK interaction between gemifloxacin and theophylline (CYP1A2, CYP2E1), omeprazole (CYP2C19), and oral contraceptives (CYP3A4). No PD interaction was demonstrated when gemifloxacin was administered concomitantly with warfarin (CYP2C9). No PK interaction was also demonstrated with digoxin.

Like the other fluoroquinolones, coadministration of Al/Mg-containing antacids and other products containing di- and tri- valent cations significantly reduced the oral bioavailability (i.e., AUC and/or Cmax) of gemifloxacin. The mechanism for this interaction is a chemical chelation with the fluoroquinolone in the gastrointestinal tract. The clinical pharmacology studies in the gemifloxacin NDA demonstrated a significant reduction in the oral bioavailability of gemifloxacin when coadministered with Maalox, Sucralfate, and Ferrous Sulfate. The timing of when each of these products could be safely administered with gemifloxacin therapy was also evaluated in these studies. For Maalox and Ferrous Sulfate, these can be a given at 3 or more hours before gemifloxacin or at 2 hours after gemifloxacin has been given. It was demonstrated that Sucralfate could be given only at 2 hours after gemifloxacin; there was still a significant reduction in gemifloxacin bioavailability at 3 hours before gemifloxacin.

Coadministration of Probenecid with gemifloxacin significantly reduced the renal clearance of gemifloxacin and increased gemifloxacin systemic exposure (i.e., AUC). This is concert with the renal elimination pathways of gemifloxacin proposed as being comprised of both filtration and active tubular secretion.

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5. Safety

a). Is there a relationship between gemifloxacin dose/exposure and the QTc interval of the ECG?

This issue was directly addressed by a **Meta analysis** performed by the sponsor of several **Clinical Pharmacology** studies from **Section 6** of the NDA to evaluate the effect of gemifloxacin **dose** on the QTc interval **(Study Report 074)**. During the NDA review, the OCPB Reviewer also requested the sponsor to perform additional analyses of the same studies used in this Meta analysis to evaluate the potential relationships between **plasma concentrations** of gemifloxacin and the change in the QTc interval. **Detailed reviews of these analyses are provided in Appendix 2.**

From a safety perspective, QTc interval data was also evaluated in patients from the Phase III efficacy and safety trials in the NDA. **Please refer to the Medical Officer's Review of Safety of gemifloxacin for a more detailed review of these QTc findings from the Phase III clinical trials.**

(i). Meta Analysis (Study Report 074)

The Meta analysis was conducted using a subset of studies from the package of **Clinical Pharmacology** studies in the NDA. To be eligible for inclusion in the Meta analysis, the individual studies were required to meet the following criteria:

1. The study required a placebo comparator.
2. The study required at least two manually read 12-lead ECG readings within the first 12 hours following dosing with gemifloxacin.

A total of 5 studies were chosen that met these criteria; brief details of these studies are provided in the tables below.

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Study Designs

Study	Study Design	Dosing Details	Study Population	Doses Studied	ECG Timepoints Post-dose
005	DB, Dose Escalation, Parallel Group	Single & Repeat (QD x 7D)	Healthy Elderly Males & Females	Placebo 320mg 480mg	1, 3, 12hrs
006	DB, Dose Escalation, Parallel Group	Single & Repeat (QD x 7D)	Healthy Young Males	Placebo 480mg 640mg	1, 12 hrs
038	DB, Parallel Group	Repeat (QD x 7D)	Healthy Young Males & Females	Placebo 320mg	1, 2, 3, 8, 12 hrs
057	DB, Dose Escalation, Crossover, with Randomized Placebo	Single	Healthy Young Females	Placebo, 320mg, 480mg, 640mg	1, 2, 3, 4, 6, 8, 12 hrs
084	DB, Dose Escalation, Crossover, with Randomized Placebo	Single	Healthy Young Japanese & Caucasian Males	Placebo, 160mg, 320mg, 640mg	1, 2, 8 hrs

Demographic Characteristics

Study	Regimen[1]	N	Mean Age. (Range) yr	Mean Weight (Range) kg	Gender (M / F)
005 (Parallel Grp)	320 mg	8	67 (64-67)	77.0 (58.9-89.1)	7 / 1
	480 mg	8	69 (66-75)	76.1 (66.6-90.7)	5 / 3
	Placebo	12	67 (60-81)	67.4 (55.8-84.5)	7 / 5
006 (Parallel Grp)	480 mg	8	29 (21-40)	78.0 (62.9-92.8)	8 / 0
	640 mg	8	29 (22-34)	77.3 (62.8-85.3)	8 / 0
	Placebo	8	29 (22-42)	75.7 (57.2-84.7)	8 / 0
038 (Parallel Grp)	320 mg	10	33 (24-44)	71.8 (53.1-93.8)	6 / 4
	Placebo	5	37 (29-41)	72.7 (56.0-79.7)	2 / 3
057 (Crossover)		12	31 (20-50)	61.7 (50.6-68.7)	0 / 12
084 (Crossover)		40	25 (19-44)	61.4 (49.0-76.0)	40 / 0
All Subjects		119	38 (19-81)	68.6 (49.0-93.8)	91 / 28

[1] – Represents regimen group for parallel group studies

The primary safety endpoint of interest was the maximum QTc interval derived from manually read 12-lead ECG's in the first 12 hours following dosing with study medication.
To estimate the effect of gemifloxacin on QTc interval, point estimates (P.E.) and the associated 90% confidence intervals (C.I.) were determined for the following comparisons of interest:

Single Dose
Gemifloxacin 320 mg – Placebo: Studies 005, 057, 084
Gemifloxacin 480 mg – Placebo: Studies 005, 006, 057
Gemifloxacin 640 mg – Placebo: Studies 006, 057, 084

Repeat Dose
Gemifloxacin 320 mg – Placebo: Studies 005, 038
Gemifloxacin 480 mg – Placebo: Studies 005, 006
Gemifloxacin 640 mg – Placebo: Studies 006
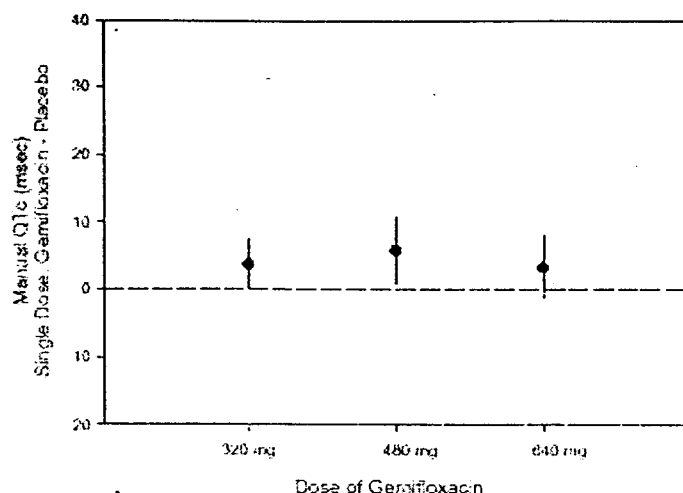
Single Dose Results
Overall, the single dose results showed that there was no clear trend for a dose response.
Single doses of 320 mg and 640 mg showed similar results with respect to the point estimates and 90% C.I., whereas the 480 mg single dose showed the greatest prolongation of maximum QTc from placebo **(see Figure and Statistical Table below).**

Meta Analysis of Maximum QTc: Single Dose Gemifloxacin vs. Placebo

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Statistical Analysis: Maximum QTc Single Dose Gemifloxacin vs. Placebo

Comparison	# of Studies (N: Gemi / Placebo)	Point Estimate	90% C. I.
320mg – Placebo	3 (55 / 12)	3.71	(0.04, 7.38)
480mg – Placebo	3 (24 / 20)	5.81	(0.88, 10.74)
640mg – Placebo	3 (54 / 8)	3.30	(-1.31, 7.92)

Statistical analyses of the individual studies / subgroups from each dose comparison showed no clear trend to implicate any one subgroup in these studies to have a greater potential for increases in the QTc interval, except for the young females in **Study 057** at 480 mg. In this study, the mean maximum increase in QTc was ~14 msec and the 90% CI indicated that increases in maximum QTc from placebo would be expected to range between 6 to 21 msec. Additionally, in the single dose study of young Japanese and Caucasian males **(Study 084)**, the Japanese males showed a P.E. for the maximum increase in QTc of 6.8 msec (95% CI -1.28, 14.98) vs. the P.E. of 0.9 msec (95% CI -6.87, 8.76) for the Caucasian males at 320 mg.
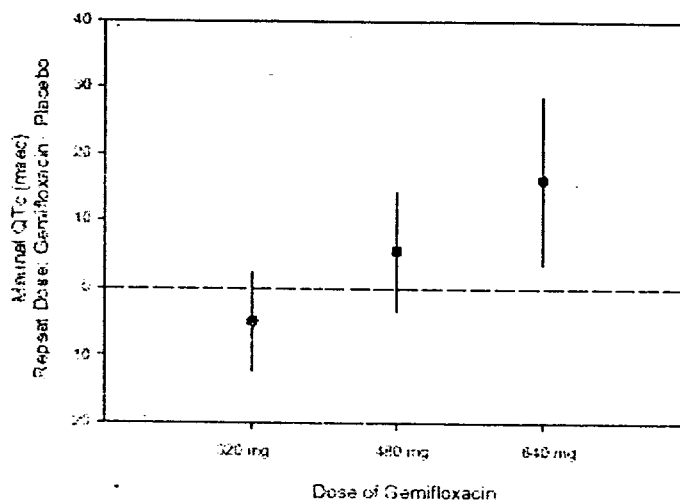
Repeat Dose Results
In contrast to the single dose results, the repeat dose results showed that there was a dose response in QTc prolongation (see Figure and Statistical Table below).

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16

Meta Analysis of Maximum QTc: Repeat Dose Gemifloxacin vs. Placebo

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Statistical Analysis: Maximum QTc Repeat Dose Gemifloxacin vs. Placebo

Comparison	# of Studies (N: Gemi / Placebo)	Point Estimate	90% C. I.
320mg – Placebo	2 (14 / 17)	-4.92	(-12.28, 2.44)
480mg – Placebo	2 (12 / 20)	5.51	(-3.29, 14.32)
640mg – Placebo	1 (8 / 8)	16.12	(3.62, 28.61)

There was an increase in the maximum QTc interval with the increase in dose, although the average change for the **320 mg dose** was a **~5 msec decrease in maximum QTc** as compared to placebo. However, there were average increases in maximum QTc of 5.5 and 16 msec, respectively, for the 480 mg and 640 mg repeated doses. Note that the lower and upper bounds of the 90% CI's also show incremental increases as the dose is increased.

The sponsor noted that the data for the 640 mg dose comparison was derived from only one study (**Study 006**) of 8 healthy male subjects and that caution should be used when interpreting these findings because of the relatively small number of subjects included with this evaluation. However, there was also an increase in the maximum QTc with the 480 mg repeated dose in this same study (P.E. 5.91; 90% CI -6.37, 18.20). Thus, there appears to be some trend for a dose response with repeated doses of gemifloxacin.

(ii). Regression Analyses

PK and 12-lead manual ECG data were used in these analyses from the same 5 Clinical Pharmacology studies used in the Meta analysis. The sponsor was requested by the OCPB Reviewer to perform 2 regression analyses:

Regression 1: Relationship between Maximum Plasma Concentration (i.e., Observed Cmax) and the Corresponding Change in QTc

Regression 2: Relationship between Plasma Concentration Corresponding to the Time of Maximal Change in QTc

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For each regression, the change in QTc was expressed as the change from each subject's baseline QTc interval (i.e., at pre-dose). This was different from the Meta analysis, which evaluated the change in QTc from placebo for each dose comparison.

Simple linear regression techniques were employed for each of the two regressions. For **Regression 1**, the ECG was not always taken at the time of the actual observed Cmax. In those instances, the QTc nearest to the time of the observed Cmax was used in the analysis.

In the sponsor's results, the sponsor chose to plot the plasma concentrations on the log scale rather than on the linear scale for both **Regressions 1 and 2**. In general, the sponsor's plots showed very weak, if any, relationship between log Cmax with change in QTc from baseline (i.e., **Regression 1**) or between log plasma concentration with the maximal change in QTc from baseline (i.e., **Regression 2**) at either single or repeat oral gemifloxacin doses. The p-values for the regressions showed non-significant differences in the slopes of the regression lines from zero and the correlation coefficients (r-values) were quite low, ranging from 0.02 to 0.13.

Regressions 1 and 2 were re-plotted by the OCPB reviewer **without log-transformation of the plasma gemifloxacin concentrations**. These plots are shown in the figures below. The regression equations are summarized as follows (p-values represent test for slope = 0):

> **Regression 1: QTc Change vs. Observed Cmax**
> Single Dose: $y = -0.97 + 0.259(x)$; $r = 0.014$; $p = 0.850$; $N=174$
> Repeat Dose: $y = 0.05 + 0.836(x)$; $r = 0.034$; $p = 0.854$; $N=31$

> **Regression 2: Maximum QTc vs. Corresponding Concentration**
> Single Dose: $y = 13.47 + 1.111(x)$; $r = 0.054$; $p = 0.485$; $N=171$
> Repeat Dose: $y = 21.72 - 0.842(x)$; $r = 0.042$; $p = 0.821$; $N=31$

Similar to the sponsor's results these regressions showed weak, if any, relationships between Cmax with change in QTc from baseline (i.e., **Regression 1**) or of plasma concentration with the maximal change in QTc from baseline (i.e., **Regression 2**) with either single or repeat oral gemifloxacin doses.

A notable observation for **Regression 2** was that the recorded times of maximum QTc changes averaged between 5 to 10 hrs postdose in the majority of subjects after both single and repeated doses. These times are substantially longer than the Tmax for gemifloxacin after oral tablet administration (i.e., mean 1.0 hr) and suggested a lag-time for the occurrence of maximum QTc changes.

OVERALL REVIEWER CONCLUSIONS – META AND REGRESSION ANALYSES:

Meta Analysis
- **Single Dose Results**
  No clear trend for dose response across all studies

  No clear trend to implicate any one subgroup of having higher maximum QTc changes, except *possibly* the young females **(Study 057)** at 480 mg and *possibly* the young Japanese males **(Study 084)** at 320 mg.

- **Repeat Dose Results**
  Some trend for dose response across all studies

  Some trend for a dose response in young male and female subjects

  No clear trend for elderly subjects from repeated doses of 320 mg to 480 mg

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Regression Analysis

- Weak (if any) relationships between the change in QTc from baseline and Cmax (i.e., **Regression 1**) or between the maximal change in QTc from baseline and the corresponding plasma concentration (i.e., **Regression 2**) with either single or repeat oral gemifloxacin doses.

- Maximum change in QTc occurred, on average, between 5 to 10 hrs postdose in the majority of subjects after both single and repeated doses – substantially longer than the Tmax for gemifloxacin after oral tablet administration (i.e., ~1.0 hr); suggesting lag-time for the occurrence of maximum QTc changes.

- In either **Regression 1 or 2**, no one subgroup (i.e., elderly, young females, young Japanese males, or young Caucasian males) clearly showed greater changes in QTc or maximum QTc. Highest maximum change in QTc was in one Japanese male (84.7 msec), but was without any reported clinically significant ECG abnormalities.

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19

Regression 1
Change in QTc From Baseline vs. Observed Cmax -
Single Oral Dose

Legend:
◇ 160 mg (N=40)
□ 320 mg (N=56)
△ 480 mg (N=24)
✕ 640 mg (N=54)

$y = 0.2594x - 0.97$
$r = 0.0144$

X-axis: Cmax (ug/mL)
Y-axis: Delta QTc from Baseline (msec)

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Regression 1
Changes in QTc from Baseline vs. Observed Cmax -
Repeat Oral Doses

y = 0.8358x + 0.05
r = 0.0344

Legend:
- ◆ 320 mg (N=13)
- ■ 480 mg (N=11)
- ▲ 640 mg (N=7)

Y-axis: Delta QTc (msec)
X-axis: Cmax (ug/mL)

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Regression 2
Maximal Change in QTc from Baseline vs. Corresponding Plasma Conc. - Single Oral Doses

Legend:
- ◇ 160 mg (N=38)
- □ 320 mg (N=56)
- △ 480 mg (N=24)
- × 640 mg (N=53)

$y = 1.1112x + 13.5$
$r = 0.0539$

X-axis: Plasma Conc. (ug/mL)
Y-axis: Delta QTc Max (msec)

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Regression 2
Maximum Change in QTc from Baseline vs. Corresponding Plasma Conc. - Repeat Oral Doses

Legend:
- ♦ 320 mg (N=13)
- ■ 480 mg (N=11)
- ▲ 640 mg (N=7)

$y = -0.842x + 21.7$
$r = 0.0424$

Y-axis: Delta QTc Max (msec)
X-axis: Plasma Conc. (ug/mL)

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B. BIOPHARMACEUTICS ISSUES

1. Is the to be marketed 320 mg gemifloxacin tablet bioequivalent to the tablet formulation used in the Phase III efficacy and safety trials?

Protocol 072 evaluated the bioequivalence of the to-be-marketed tablet relative to the Phase III tablet in 22 healthy male and female subjects. The to-be-marketed tablet batch was of biobatch size. **The to-be-marketed 320 mg tablet formulation of gemifloxacin was shown to be bioequivalent to the Phase III Clinical Trials 320 mg tablet, as evidenced by the point estimates and 90% CI for AUC(0-inf) (0.89 (0.81, 0.98)) and Cmax (0.92 (0.81, 1.05)) completely contained within the equivalence range of 0.80 to 1.25.**

Two additional BA/BE studies (**055 and 034**) also demonstrated adequate "bio-links" between the early Phase I and Phase II capsule formulations and between the Phase II capsule and Phase III tablet formulations.

2. What are the physical / chemical characteristics of gemifloxacin (i.e., the drug substance) that are particularly relevant from a Biopharmaceutics perspective?

All of the information regarding drug solubility, partition coefficient, pKa values, etc., which is generally included in the Chemistry, Manufacturing, and Controls Section (Item 4, CMC) of the NDA was not provided. Instead, this information was cross-referenced to the Drug Master File (DMF ——— and was not available to the OCPB Reviewer. Some limited information on gemifloxacin solubility was provided in the CMC section. The aqueous solubility of gemifloxacin at 37°C and 20°C varied with pH (pH range 1.4-10.4), with the lowest solubility occurring at pH between 6.4 to 8.5 and the highest solubility occurring at low pH from 1.4 to 5.0.

3. Was gemifloxacin classified according to the Biopharmaceutics Classification System (BCS)?

No information regarding BCS classification of gemifloxacin could be located in the NDA. Although this information *may* be contained within the DMF ——— mentioned above, the sponsor made no reference to BCS classification in this NDA for gemifloxacin.

C. FORMULATION INFORMATION AND IN VITRO DISSOLUTION

Gemifloxacin 320 mg Tablet

The proposed commercial product is an immediate release 320 mg white, film-coated, oval debossed tablet with breaklines on both faces that is to be supplied both in HDPE bottles and blister packs. The commercial product, *Factive 320 mg tablets*, contain gemifloxacin mesylate (SB-265805-S) as the sesquihydrate form of gemifloxacin free base (SB-265805). The molecular weight of the pure free base (pfb) is 76.0% of the gemifloxacin mesylate sesquihydrate. The quantitative composition of the to-be-marketed 320 mg immediate release tablets is provided in the table below.

24

Composition of the 320 mg Gemifloxacin Commercial Tablet (Unit Formula)

	Specification	Function	Quantity/Tablet (mg)
Active Ingredient			
Gemifloxacin mesylate*		Active ingredient	426.39
Inactive Ingredients			
Microcrystalline Cellulose	NF		
Povidone	USP		
Crospovidone	NF		
Magnesium Stearate	NF		
Purified Water	USP		
Total Weight of Tablet Core			
	Non-Compendial		
Purified Water	USP		
Total Weight of Tablet			533.0 mg

* Gemifloxacin mesylate is the sesquihydrate form; 426.39 mg is equivalent to 320 mg pure free base

In Vitro Dissolution

The proposed dissolution method and specification are as follows:

Medium	0.01M HCl
Volume	900 mL
Temperature	37°C ± 0.5°C
Apparatus	USP Apparatus No. 2 – Paddle
Paddle Speed	50 rpm
Specification	Not less than ⎯⎯ of label claim released (Q = ⎯⎯) at 30 minutes

The table below summarizes the dissolution data at **30 minutes** for 3 stability and 3 qualification batches, and two additional tablet batches used in the BE studies. The raw dissolution data from these tablet batches are provided and reviewed in greater detail in **Appendix 3**. In all cases the proposed dissolution method and conditions were used to generate this data. i.e., USP Apparatus 2 (paddle) at 50 RPM in 900 mL 0.01 M HCl.

Percent Dissolution for Gemifloxacin 320 mg Tablets at 30 Minutes

	Stability N98145	Stability N98146	Stability N98196	Qual. N99112	Qual. N99115	Qual. N99116	BE 034 N98072	Pivotal BE 072 N98144
Mean*	97.2	99.0	98.1	99.4	94.0	95.0	100.9	101.7
SD	4.4	2.1	2.9	1.0	5.1	4.6	1.4	1.0
%CV								
Range								

*N = 6 for Qualification Batches (Qual.) and BE Study Batches; N=12 for Stability Batches

Overall, the data showed adequate dissolution of all batches. At 30 minutes dissolution exceeded the proposed specification of NLT ⎯% dissolved at 30 minutes. As can be seen from the table above, mean dissolution at 30 minutes was 94% or greater and ranged from ⎯⎯⎯ ⎯⎯ across all batches.

Although the dissolution medium (0.01 M HCl) and conditions (USP Apparatus 2 at 50 RPM) are adequate and the sponsor provided adequate rationale and an adequate developmental history for the method in the NDA, the proposed specification should be tightened to Q = ⎯⎯ (NLT ⎯% dissolved) at 30 minutes. This recommendation is based on the dissolution data that was provided by the sponsor.

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D.   OTHER INFORMATION

1. Assay Methods

Gemifloxacin concentrations in plasma, urine, and other biological matrices were determined using ⸺⸺ methods that employed ⸺⸺⸺⸺ Both plasma and urine assays for gemifloxacin were adequately validated over linear ranges from ⸺⸺ µg/mL, with the LLOQ at ⸺⸺⸺ The linear ranges for the other matrices varied, but were also adequately validated. The performance of all gemifloxacin assays was acceptable as evidenced by the results of the quality control samples (low, medium, and high) all within ±15% for both precision and accuracy during study sample analysis. For some Clinical Pharmacology studies, the plasma concentrations of the individual (+) and (−) gemifloxacin enantiomers were also determined using a ⸺⸺⸺ method that employed ⸺⸺⸺ ionization. This method was adequately validated over the linear range from ⸺⸺ ⸺, with the LLOQ at ⸺⸺ for each enantiomer. The performance of this assay was also acceptable.

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IV.   RECOMMENDATION

Item 6 of **NDA 21-158** for gemifloxacin 320 mg tablets (FACTIVE®) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and was deemed to be acceptable. The comments outlined below are to be conveyed to the sponsor. The Clinical Pharmacology and Biopharmaceutics comments for the proposed label are contained within the label as **Appendix 1.**

V.   COMMENTS FOR THE SPONSOR

1. It is recommended that the proposed *in vitro* tablet dissolution specification of Q = ⎯⎯ (NLT ⎯⎯ of label claim released) at 30 minutes be changed to Q = ⎯⎯ (NLT ⎯⎯ of label claim released) at 30 minutes. This recommendation is based on the dissolution data that was provided by the sponsor for the stability and qualification tablet batches, as well as the tablet batches used in the Bioequivalence/Bioavailability Studies 072 and 034.

2. From the **Regression Analyses of QTc Interval** and gemifloxacin plasma concentrations (i.e., **Regression 1 and Regression 2**), please provide the individual subject data for the placebo treatment in the same manner as with the gemifloxacin treatment. That is, we would like the change in the QTc interval from baseline at the time of gemifloxacin Cmax (i.e., approximately 1 hr) for all of the placebo treated subjects from **Regression 1**. We would also like the maximum change in the QTc from baseline for all of the placebo treated subjects from **Regression 2**. This placebo data should be provided as a hard copy and also electronically in the same format as the gemifloxacin treatment data from the 5 Clinical Pharmacology studies (i.e., EXCEL spreadsheet).

VI.   LABELING COMMENTS – SEE APPENDIX 1   APPEARS THIS WAY
                                                    ON ORIGINAL

VII.   POTENTIAL PHASE 4 STUDIES

1. In the **Hepatic Impairment Study 032**, only 3 subjects with severe hepatic impairment (Child-Pugh Class C) could be studied. This number of subjects is insufficient to adequately evaluate the pharmacokinetics of gemifloxacin in severe hepatic impairment. In order to adequately characterize the PK of gemifloxacin and provide for more complete labeling on the use of gemifloxacin for patients with hepatic impairment, we recommend that a study be conducted to compare the PK and safety of gemifloxacin in a group of severe hepatic impairment subjects/patients versus a group of demographically matched subjects with normal hepatic function in the same study.

2. In the **Drug-Drug Interaction Study 040** with **Sucralfate**, the results demonstrated that sucralfate can be administered 2 hours after taking gemifloxacin, but sucralfate cannot be taken 3 hours before gemifloxacin. However, it is not known how much longer than 3 hours before gemifloxacin would it be acceptable to administer sucralfate. Thus, in order to provide more adequate labeling information regarding the use of sucralfate with gemifloxacin, we recommend that a study be conducted to further evaluate the timing of sucralfate dosing before the administration of gemifloxacin.

3. The potential for gemifloxacin to prolong the QT interval needs to be further evaluated in Clinical Pharmacology studies of otherwise healthy young ($\geq$18 to 64 years) and elderly ($\geq$65 years) male and female subjects. It is recommended that the studies be designed to:
    1) Assess the effect of single escalating oral doses of gemifloxacin (320 mg, 640 mg, and 960 mg) and placebo on the QTc interval (i.e., Study 1: Noncomparative, Single Dose Escalation, Crossover, Placebo Controlled Study);

27

2) Compare the potential QTc prolonging effect of a single oral clinical dose of gemifloxacin (320 mg) with that of placebo and of other fluoroquinolone antibiotics, for example, gatifloxacin, moxifloxacin, levofloxacin, ciprofloxacin, sparfloxacin (i.e., Study 2: Comparative, Single Dose, Crossover, Placebo Controlled Study).

3) Compare the effect of repeat oral doses of gemifloxacin at steady state (320 mg Q24 hr x 7 days) with that of repeat oral doses of a fluoroquinolone comparator at steady state (e.g., gatifloxacin, moxifloxacin, levofloxacin, or ciprofloxacin) on the QTc interval (i.e., Study 3: Comparative, Repeat Dose, Crossover Study).

/S/

[   ] /2/11/00

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

/S/

RD/FT signed by Funmi Ajayi, Ph.D (TL) [   ] 12/11/00
CP/B Briefing (12/7/00) Attendees: F. Ajayi, J. Lazor, A. Selen, F. Pelsor, J. Powers, E. Cox, R. Patniak

cc:
Div. File (HFD-590): NDA 21-158
HFD-590 (J. Powers, MO)
HFD-590 (B. Leissa, TL/MO)
HFD-590 (L. Kimzey, PM/CSO)
//
//
HFD-205 (FOI)
HFD-880 (F. Ajayi, TL)

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APPENDIX 1:

PROPOSED LABELING WITH
FDA COMMENTS AND CHANGES
[V: 10/25/00]

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29 Pages have been redacted in full from this document

Reason:

_____ b(2) 'low'

___✗___ b(4) CCI

_____ b(4) TS

_____ b(5) Deliberative Process: Attorney Client and Attorney Work Product Privilege

_____ b(6) Personal Privacy

_____ b(7) Law Enforcement Records

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT LG Life Sciences, Ltd.	DATE OF SUBMISSION October 4, 2002
TELEPHONE NO. (Include Area Code) (781) 487-9900	FACSIMILE (FAX) Number (Include Area Code) (781) 487-0525
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): LG Life Sciences, Ltd. 25th Floor, LG Twin Tower East, 20, Yoido-dong, Youngdungpo-gu Seoul 150-721, Korea	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE PAREXEL International 195 West Street Waltham, MA 02451 Phone: 781-487-9900 Fax: 781-487-0525

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-158

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) gemifloxacin mesylate	PROPRIETARY NAME (trade name) IF ANY FACTIVE®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (±)-7-[3-(aminomethyl)-4-methyl-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-1, 8-naphthyridine-3-carboxylic acid, 7^4-(Z)-(O-methyloxime), monomethanesulfonate	CODE NAME (If any) SB-265805 or LB-20304a
DOSAGE FORM: Tablet	STRENGTHS: 320 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: Treatment of infections caused by susceptible strains of designated organisms in the following conditions: acute exacerbations of chronic bronchitis and community-acquired pneumonia

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50)   ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	☒ 505 (b)(1)	☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug   Holder of Approved Application

TYPE OF SUBMISSION (check one)   ☐ ORIGINAL APPLICATION   ☐ AMENDMENT TO A PENDING APPLICATION   ☒ RESUBMISSION

☐ PRESUBMISSION   ☐ ANNUAL REPORT   ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT   ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT   ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT   ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:_____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY   ☐ CBE   ☐ CBE-30   ☐ Prior Approval (PA)

REASON FOR SUBMISSION Complete response to FDA's 'not approvable' letter of December 15, 2000

PROPOSED MARKETING STATUS (check one)   ☒ PRESCRIPTION PRODUCT (Rx)   ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 DLT/234 paper	THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Not applicable. Refer to the original NDA 21-158 submission (December 15, 1999) for complete CMC/Establishment information.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 21-376

FORM FDA 356h (4/00)   PAGE 1

This application contains the following items: *(Check all that apply)*		
☒	1.	Index
☒	2.	Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3.	Summary (21 CFR 314.50(c))
☒	4.	Chemistry section
☒		A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐		B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐		C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5.	Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6.	Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☒	7.	Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8.	Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☒	9.	Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10.	Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11.	Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12.	Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
☒	13.	Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
☐	15.	Establishment description (21 CFR Part 600, if applicable)
☒	16.	Debarment certification (FD&C Act 306(k)(1))
☐	17.	Field copy certification (21 CFR 314.50(k)(3))
☐	18.	User Fee Cover Sheet (Form FDA 3397)
☒	19.	Financial Information (21 CFR Part 54)
☐	20.	OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Alberto Grignolo, Ph.D., Senior Vice President and General Manager, Worldwide Regulatory Affairs	Oct. 4, 2002
ADDRESS *(Street, City, State, and ZIP Code)* PAREXEL International 195 West Street, Waltham, MA 02451		TELEPHONE NUMBER (781) 487-9900

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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NDA 21-158

FACTIVE® (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

**APPEARS THIS WAY
ON ORIGINAL**

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey