

7.6 µg.h/mL for combined sexes). These findings were associated with deposits of crystalline drug-related material, also containing magnesium, in bile canaliculi and bile ducts. Elevated hepatic enzymes, most consistently ALT and alkaline phosphatase, but also GGT and AST, were also associated with the liver histopathology. The abnormalities in hepatic enzymes returned to normal following a four week off-dose period. The no-effect dose for hepatic effects after 28 days was 96 mg/kg/day (mean C_{max} 4.1 µg/mL, AUC 29.2 µg.h/mL for combined sexes), and after 6 months was 8 mg/kg/day (mean C_{max} 0.64 µg/mL, AUC 3.0 µg.h/mL). The values for humans dosed with 320 mg of gemifloxacin orally are C_{max} 1.2 µg/mL and AUC 8.4 µg.h/mL, respectively.

Clinical Pharmacology - Oral Gemifloxacin-NDA

In clinical pharmacology studies, repeat doses of gemifloxacin 320mg were well tolerated, but repeat doses of 480mg and 640mg resulted in an increase in the rate of asymptomatic elevations of ALT and AST relative to the 320mg dose. These abnormalities returned to normal within 48 hours following cessation of dosing. All of the abnormalities in LFTs in these studies at all doses were considered of mild or moderate severity by the investigators.

Table 41. Incidence of Flagged LFT's at Various Doses on Gemifloxacin in a Clinical Pharmacology Study

| Parameter | Flag | Gemifloxacin dose (mg) | | | | All doses |
|-----------|------|------------------------|------------|-------------|------------|-------------|
| | | <320 | 320 | 480-600 | ≥640 | |
| | | n/N (%) | n/N (%) | n/N (%) | n/N (%) | n/N (%) |
| ALT | High | 0/16 (0.0) | 0/79 (0.0) | 5/16 (31.2) | 1/8 (12.5) | 6/119 (5.0) |
| AST | High | 0/16 (0.0) | 1/79 (1.2) | 3/16 (18.7) | 1/8 (12.5) | 5/119 (4.2) |

Source: Adapted from Table DS16B from NDA 21-158 ISS

In single dose studies with gemifloxacin 320mg, the only LFT with F3 transitions was high total bilirubin [3/373 subject sessions (0.8%)]. Subject 066.001.00015 had a total bilirubin value of 7.5 mg/dL (normal range: 0-1.0 mg/dL) 7 days after single dose gemifloxacin 320mg. The increase was 7.5 x ULN and was suspected to be related to study medication. It was therefore reported as an adverse experience (bilirubinemia). At screening, the subject's total bilirubin was normal (0.8 mg/dL). The subject also had mildly elevated bilirubin 7 days after dosing with ofloxacin 400mg (1.7 mg/dL), which occurred before the gemifloxacin dosing session. At follow-up, the subject's bilirubin value had returned to just outside the normal reference range (1.1 mg/dL), but was not considered clinically significant by the investigator. The patient was asymptomatic. Two further subjects (084.001.00034 and 084.001.00035) had high total bilirubin F3 transitions after single dose gemifloxacin 320mg, each less than 2 x ULN, which were not considered clinically significant by the investigators.

Four elderly subjects were withdrawn from one study (study 005, a pK study in healthy elderly subjects) during repeat dosing with gemifloxacin 480mg because of asymptomatic, reversible increases in ALT (subjects 005.001.015, 005.001.019, 005.001.020 and 005.001.022) and AST (005.001.019 and 005.001.022), which were elevated outside an extended normal range on two consecutive occasions during the study in each patient. These increases LFTs occurred after 5 to 7 days of dosing and peak values ranged from 121 to 333 IU/L for ALT (reference range: 0-55.99 IU/L) and 94 to 227 IU/L for AST (reference range: 0-46.99 IU/L). An additional subject (subject 005.001.018) who received gemifloxacin 480mg completed the study despite asymptomatic increases in AST and ALT (peak values of 78 and 148 IU/L, respectively).

In addition, 2/12 subjects who received placebo and 1/8 subjects who received gemifloxacin 320mg in the same study had increases in ALT above the upper limit of the normal with peak values of 103 (subject 005.001.00006, day 8), 83 (subject 005.001.00013, day 8) and 74 IU/L (subject 005.001.00010, day 8), respectively. One of the subjects who received placebo (subject 005.001.00013) also had increased AST levels (59 IU/L) on day 8). All abnormal transaminases for these subjects decreased within 48 hours of discontinuing study medication, and all values were within the normal range at follow-up.

In clinical pharmacology studies, repeat doses of gemifloxacin 320mg were well tolerated, but repeat doses of 480mg and 640mg resulted in an increase in the rate of asymptomatic elevations of ALT and AST relative to the 320mg dose. These abnormalities returned to normal within 48 hours following cessation of dosing. All of the abnormalities in LFTs in these studies at all doses were considered of mild or moderate severity by the investigators.

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Table 42. Incidence of Flagged LFT's at various doses on Gemifloxacin in a Clinical Pharmacology Study

| Parameter | Flag | Gemifloxacin dose (mg) | | | | |
|-----------------|------|------------------------|------------|-------------|------------|-------------|
| | | <320 | 320 | 480-600 | ≥640 | All doses |
| | | n/N (%) | n/N (%) | n/N (%) | n/N (%) | n/N (%) |
| ALT | High | 0/16 (0.0) | 0/79 (0.0) | 5/16 (31.2) | 1/8 (12.5) | 6/119 (5.0) |
| AST | High | 0/16 (0.0) | 1/79 (1.2) | 3/16 (18.7) | 1/8 (12.5) | 5/119 (4.2) |
| Total Bilirubin | High | 0/16 (0.0) | 1/79 (1.2) | 0/16 (0.0) | 0/8 (0.0) | 1/119 (0.8) |
| Glucose | Low | 0/16 (0.0) | 1/79 (1.2) | 0/16 (0.0) | 0/8 (0.0) | 1/119 (0.8) |
| Potassium | Low | 0/16 (0.0) | 1/79 (1.2) | 0/16 (0.0) | 0/8 (0.0) | 1/119 (0.8) |

Data Source: ISS Table DS16B.

The rate of LFT abnormalities with the higher doses of gemifloxacin is higher than with the 320 mg doses. This is also the reason for the discrepancies seen in Table 12 where except for one subject with a bilirubin elevated to >8x ULN. There were no elevations of LFTs >4xULN in the 320 mg dose studies but a few other notable elevations are seen in the All Studies section which includes higher doses as well.

The rate of LFT elevations in the clinical pharmacology studies for all doses was less than 1.0% for gemifloxacin. The frequency of ALT and AST transitions >2 x ULN was similar for gemifloxacin and comparators but greater than for placebo. The frequency of LFT transitions >2 x upper limit of normal (ULN) in the clinical. The frequency of total bilirubin transitions >2 x ULN was similar for gemifloxacin (0.9%, 6/694) and for placebo (0.7%, 1/138). A formal Phase 1 study (study 032) was conducted in 23 subjects with varying degrees of hepatic impairment (categorized on the basis of Child-Pugh classification into Group A: mild hepatic impairment, Group B: moderate hepatic impairment and Group C: severe hepatic impairment). The study included three normal, healthy subjects (Group D) who were matched by group for age, weight and sex to the Child-Pugh C group (severe). All subjects in Group A (mild), Group B (moderate) and Group D (healthy subjects) received single oral doses of 320mg gemifloxacin. All three subjects in Group C (severe) received single oral doses of 160mg gemifloxacin. There were no withdrawals or deaths, but there were two serious AEs reported during this study. The SAEs were gastrointestinal hemorrhage and portal hypertension. The investigators considered both SAEs as related to the patients' underlying liver disease.

Clinical Pharmacology Studies-Intravenous Gemifloxacin

In non-patient volunteers receiving a single dose of intravenous gemifloxacin 250mg infused over 1 hour for 7 days, the rate of hepatic function abnormalities was higher than in the oral studies. The rates of increased LFTs, however, were similar in the gemifloxacin IV group and the placebo group. Increases in ALT above the upper limit of normal (maximum value 154 IU/ml, normal range 0-44 IU/ml) were seen in 6/20 subjects receiving 250mg intravenous gemifloxacin daily for up to 7 days and 7/20 subjects receiving placebo. Changes of potential clinical concern that exceeded twice the upper limit of normal range were seen in 3/20 subjects receiving gemifloxacin and no subjects receiving placebo. These changes were asymptomatic and were not associated with other laboratory abnormalities. The changes in LFT's resolved towards baseline

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Clinical Studies

Hepatic Effects at Higher Doses

Included in the NDA submission 21-158 are studies of uncomplicated UTI where single doses of 640 mg were compared to ciprofloxacin 250 mg po bid for 3 days in primarily otherwise healthy young women. The LFT abnormalities by treatment arm are shown in the table below. For all LFT measurements there were higher rates of abnormalities in the gemifloxacin arm. These differences had mostly resolved by the end of therapy (note-gemifloxacin was administered as a single dose.)

Table 43. Number (%) of Patients with Liver Function Values in the Specified Ranges at the On-Therapy Visit (Gemifloxacin 640mg vs Ciprofloxacin 250mg, Patients In-Range at Screening)

| Functional Group/ Variable | Range | Treatment Group | | | |
|-------------------------------|------------|--|--------|--|--------|
| | | Gemifloxacin 640mg Single Dose N =638 | | Ciprofloxacin 250mg bid N = 662 | |
| | | n/N* | (%) | n/N* | (%) |
| ALT | <ULN | 569/592 | (96.1) | 600/606 | (99.0) |
| | ULN-<2xULN | 14/592 | (2.4) | 6/606 | (1.0) |
| | 2-<4xULN | 4/592 | (0.7) | 0/606 | |
| | 4-<6xULN | 1/592 | (0.2) | 0/606 | |
| | 6-<8xULN | 3/592 | (0.5) | 0/606 | |
| | ≥8xULN | 1/592 | (0.2) | 0/606 | |
| AST | <ULN | 578/593 | (97.5) | 602/607 | (99.2) |
| | ULN-<2xULN | 10/593 | (1.7) | 5/607 | (0.8) |
| | 2-<4xULN | 3/593 | (0.5) | 0/607 | |
| | 4-<6xULN | 1/593 | (0.2) | 0/607 | |
| | 6-<8xULN | 0/593 | | 0/607 | |
| | ≥8xULN | 1/593 | (0.2) | 0/607 | |
| ALK-P | <ULN | 599/606 | (98.8) | 622/625 | (99.5) |
| | ULN-<2xULN | 7/606 | (1.2) | 3/625 | (0.5) |
| | 2-<4xULN | 0/606 | | 0/625 | |
| | 4-<6xULN | 0/606 | | 0/625 | |
| | 6-<8xULN | 0/606 | | 0/625 | |
| | ≥8xULN | 0/606 | | 0/625 | |
| Total | <ULN | 596/600 | (99.3) | 610/615 | (99.2) |
| Bilirubin | ULN-<2xULN | 4/600 | (0.7) | 5/615 | (0.8) |
| | 2-<4xULN | 0/600 | | 0/615 | |
| | 4-<6xULN | 0/600 | | 0/615 | |
| | 6-<8xULN | 0/600 | | 0/615 | |
| | ≥8xULN | 0/600 | | 0/615 | |

Data Source: Applicant Table 370 from NDA 21-158 ISS

*n/N= number of patients outside limit/number of patients evaluated for the particular parameter

(Note: 2/4 patients treated with gemifloxacin and 0/5 patients treated with ciprofloxacin who had bilirubin elevations to 2-4xULN had treatment emergent elevations.

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Table 44. Number (%) of Patients with Liver Function Values in the Specified Ranges at the End of Therapy Visit (Gemifloxacin 640mg vs Ciprofloxacin 250mg, Patients In-Range at Screening)

| Functional Group/ Variable | Range | Treatment Group | | | |
|-------------------------------|------------|---|--------|--|---------|
| | | Gemifloxacin 640mg Single Dose N = 638 | | Ciprofloxacin 250mg bid N = 662 | |
| | | n/N* | (%) | n/N* | (%) |
| ALT | <ULN | 577/585 | (98.6) | 582/588 | (99.0) |
| | ULN-<2xULN | 7/585 | (1.2) | 6/588 | (1.0) |
| | 2-<4xULN | 1/585 | (0.2) | 0/588 | |
| | 4-<6xULN | 0/585 | | 0/588 | |
| | 6-<8xULN | 0/585 | | 0/588 | |
| | ≥8xULN | 0/585 | | 0/588 | |
| AST | <ULN | 582/585 | (99.5) | 579/588 | (98.5) |
| | ULN-<2xULN | 3/585 | (0.5) | 9/588 | (1.5) |
| | 2-<4xULN | 0/585 | | 0/588 | |
| | 4-<6xULN | 0/585 | | 0/588 | |
| | 6-<8xULN | 0/585 | | 0/588 | |
| | ≥8xULN | 0/585 | | 0/588 | |
| ALK-P | <ULN | 593/594 | (99.8) | 602/602 | (100.0) |
| | ULN-<2xULN | 1/594 | (0.2) | 0/602 | |
| | 2-<4xULN | 0/594 | | 0/602 | |
| | 4-<6xULN | 0/594 | | 0/602 | |
| | 6-<8xULN | 0/594 | | 0/602 | |
| | ≥8xULN | 0/594 | | 0/602 | |
| Total | <ULN | 584/589 | (99.2) | 588/596 | (98.7) |
| Bilirubin | ULN-<2xULN | 5/589 | (0.8) | 8/596 | (1.3) |
| | 2-<4xULN | 0/589 | | 0/596 | |
| | 4-<6xULN | 0/589 | | 0/596 | |
| | 6-<8xULN | 0/589 | | 0/596 | |
| | ≥8xULN | 0/589 | | 0/596 | |

The remainder of the LFT abnormalities from the clinical studies will be discussed as part of the combined population.

The Clinical Studies Combined Population

During the On-Therapy visit in the combined population, 0.8% of the gemifloxacin treated patients had ALT elevations >2xULN in comparison to 0.5% for comparator. Only 1 patient in each arm had an ALT value >4xULN with the comparator patient's level being higher than 8xULN (Patient number 011.015.05219). At the On-Therapy visit, 0.7% of gemifloxacin patients had AST levels >2xULN while 0.4% of comparator patients achieved this level of abnormality. Two gemifloxacin patients had AST values >4xULN (008.042.12183 and 008.044.12476) while one comparator did so (012.135.17939). There was only 1 gemifloxacin patient (013.101.02888) with an alkaline phosphatase >4xULN and no comparator treated patients. There were 3 gemifloxacin treated patients with bilirubin elevations of >2xULN in comparison to none for comparator (Table 45.)

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In the Combined Population 2 patients in each treatment group (gemifloxacin and comparator) had end of therapy treatment emergent elevations of >4xULN for ALT. There were no elevations of >4xULN for any other hepatic parameter measured at the end of treatment for either arm. Please see Table 45.

Table 45. Number (%) of Patients with Liver Function Tests Within Specified Ranges at the On-Therapy Visit - Patients In-Range at Screening (Combined Population)

| Functional Group/ Variable | | Treatment Group | | | |
|-------------------------------|----------------|---|--------|---|--------|
| | | Gemifloxacin 320mg qd N=6681* n/Np ⁺ | | All Comparators N=5174* n/Np ⁺ | |
| Range | | | (%) | | (%) |
| ALT | <ULN | 3800/3989 | (95.3) | 3443/3588 | (96) |
| | ULN- <2xULN | 162/3989 | (4.1) | 127/3588 | (3.5) |
| | 2-<4xULN | 26/3989 | (0.7) | 15/3588 | (0.4) |
| | 4-<6xULN | 1/3989 | (<0.1) | 2/3588 | (0.1) |
| | 6-<8xULN | 0/3989 | | 0/3588 | |
| | ≥8xULN | 0/3989 | | 1/3588 | (<0.1) |
| AST | <ULN | 3824/3990 | (95.8) | 3512/3633 | (96.7) |
| | ULN- <2xULN | 141/3990 | (3.5) | 106/3633 | (2.9) |
| | 2-<4xULN | 25/3990 | (0.6) | 14/3633 | (0.4) |
| | 4-<6xULN | 1/3990 | (<0.1) | 1/3633 | (<0.1) |
| | 6-<8xULN | 1/3990 | (<0.1) | 0/3633 | |
| | ≥8xULN | 0/3990 | | 0/3633 | |
| Alkaline Phosphatase | <ULN | 4007/4075 | (98.3) | 3607/3672 | (98.2) |
| | ULN- <2xULN | 61/4075 | (1.5) | 62/3672 | (1.7) |
| | 2-<4xULN | 7/4075 | (0.1) | 3/3672 | (0.1) |
| | 4-<6xULN | 1/4075 | (<0.1) | 0/3672 | (<0.1) |
| | 6-<8xULN | 0/4075 | | 0/3672 | |
| | ≥8xULN | 0/4075 | | 0/3672 | |
| Total Bilirubin | <ULN | 4046/4087 | (99) | 3621/3655 | (99.1) |
| | ULN- <2xULN | 38/4087 | (0.9) | 34/3655 | (0.9) |
| | 2-<4xULN | 3/4087 | (0.1) | 0/3655 | |
| | 4-<6xULN | 0/4087 | | 0/3655 | |
| | 6-<8xULN | 0/4087 | | 0/3655 | |
| | ≥8xULN | 0/4087 | | 0/3655 | |

Data Source: Table 206a.

* N = total number of patients with in-range (<ULN) values at screening.

+ n/Np = number of patients within the specified range/number of patients evaluated for the laboratory parameter.

Source: Adapted from Applicant's Table 17.27 from NDA 21-158, 18-month Safety Update

Table 46. Number (%) of Patients with Liver Function Tests Within Specified Ranges at the End-of-Therapy Visit - Patients In-Range at Screening (Combined Population)

| Functional Group/ Variable | Range | Treatment Group | | | |
|-------------------------------|------------|----------------------------------|--------|----------------------------|--------|
| | | Gemifloxacin 320mg od N=6681* | | All Comparators N=5174* | |
| | | n/Np ⁺ | (%) | n/Np ⁺ | (%) |
| ALT | <ULN | 4752/4967 | (95.7) | 3545/3709 | (95.6) |
| | ULN-<2xULN | 191/4967 | (3.8) | 135/3709 | (3.6) |
| | 2-<4xULN | 22/4967 | (0.4) | 27/3709 | (0.7) |
| | 4-<6xULN | 2/4967 | (<0.1) | 2/3709 | (0.1) |
| | 6-<8xULN | 0/4967 | | 0/3709 | |
| | ≥8xULN | 0/4967 | | 0/3709 | |
| AST | <ULN | 4892/5004 | (97.8) | 3673/3751 | (97.9) |
| | ULN-<2xULN | 99/5004 | (2) | 72/3751 | (1.9) |
| | 2-<4xULN | 13/5004 | (0.3) | 6/3751 | (0.2) |
| | 4-<6xULN | 0/5004 | | 0/3751 | |
| | 6-<8xULN | 0/5004 | | 0/3751 | |
| | ≥8xULN | 0/5004 | | 0/3751 | |
| Alkaline Phosphatase | <ULN | 5006/5079 | (98.6) | 3712/3778 | (98.3) |
| | ULN-<2xULN | 69/5079 | (1.4) | 64/3778 | (1.7) |
| | 2-<4xULN | 4/5079 | (0.1) | 2/3778 | (0.1) |
| | 4-<6xULN | 0/5079 | | 0/3778 | |
| | 6-<8xULN | 0/5079 | | 0/3778 | |
| | ≥8xULN | 0/5079 | | 0/3778 | |
| Total Bilirubin | <ULN | 5009/5081 | (98.6) | 3703/3753 | (98.7) |
| | ULN-<2xULN | 69/5081 | (1.4) | 50/3753 | (1.3) |
| | 2-<4xULN | 3/5081 | (0.1) | 0/3753 | |
| | 4-<6xULN | 0/5081 | | 0/3753 | |
| | 6-<8xULN | 0/5081 | | 0/3753 | |
| | ≥8xULN | 0/5081 | | 0/3753 | |

Source Table 3.71 from NDA 21-158 18 Month Safety Update

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Patients with Baseline Liver Disease (All Therapeutic Indications)

Patients with an ongoing medical history of liver disease or a baseline AE suggestive of active liver disease were included in a population of patients defined as having liver disease at baseline. Patients were excluded from the population of patients with liver disease if they had a past history of liver disease but did not have active liver disease at baseline.

In the Combined population, 58.7% (138/235) of patients with baseline liver disease in the gemifloxacin group and 54.8% (92/168) of patients with baseline liver disease in the all-comparators group reported at least one adverse experience (AE). Adverse experiences associated with the hepatobiliary system were reported in 16.6% (39/235) of patients in the gemifloxacin group and 11.3% (19/168) of patients in the all-comparators group. The most frequently reported AEs among patients with baseline liver disease in the gemifloxacin group were SGPT increased (7.2%), SGOT increased (5.1%), abdominal pain (4.7%), diarrhea (4.7%), and thrombocythemia (4.7%).

The hepatobiliary AE's for which there were differences between the gemifloxacin group and comparator group include hepatic enzymes increased and SGPT increased, alkaline phosphatase increased (4.3% for gemifloxacin patients and 0% for comparator), and bilirubinemia (2.1% for gemifloxacin group and 0.6% for comparator). The gemifloxacin group contains some patients from non-comparative studies.

The non hepatobiliary AE's which were more prominent in the gemifloxacin group included anemia, myalgia, CPK increased, hypokalemia, and leukopenia. The AE's which were more prominent in the comparator group were diarrhea, vomiting, and dizziness.

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Table 47. Number (%) of Patients with the Most Frequently Occurring ($\geq 1\%$) Adverse Experiences in Patients with Baseline Liver Disease (Combined)

| Preferred Term | Treatment Group | | | |
|-------------------------------------|--------------------------------|--------|--------------------------|--------|
| | Gemifloxacin 320mg qd N=235 | | All Comparators N=168 | |
| | n | (%) | n | (%) |
| Patients with at least 1 AE | 138 | (58.7) | 92 | (54.8) |
| SGPT Increased | 17 | (7.2) | 8 | (4.8) |
| SGOT Increased | 12 | (5.1) | 8 | (4.8) |
| Abdominal Pain | 11 | (4.7) | 4 | (2.4) |
| Diarrhea | 11 | (4.7) | 21 | (12.5) |
| Thrombocythemia | 11 | (4.7) | 4 | (2.4) |
| Hyperglycemia | 10 | (4.3) | 4 | (2.4) |
| Phosphatase Alkaline Increased | 10 | (4.3) | 0 | |
| Headache | 9 | (3.8) | 3 | (1.8) |
| Hepatic Enzymes Increased | 8 | (3.4) | 0 | |
| Rash | 8 | (3.4) | 5 | (3.0) |
| Anemia | 7 | (3.0) | 2 | (1.2) |
| Nausea | 7 | (3.0) | 6 | (3.6) |
| Myalgia | 6 | (2.6) | 1 | (0.6) |
| Back Pain | 5 | (2.1) | 2 | (1.2) |
| Bilirubinemia | 5 | (2.1) | 1 | (0.6) |
| Chest Pain | 5 | (2.1) | 5 | (3.0) |
| CPK Increased | 5 | (2.1) | 2 | (1.2) |
| Fever | 5 | (2.1) | 2 | (1.2) |
| Insomnia | 5 | (2.1) | 3 | (1.8) |
| Dizziness | 4 | (1.7) | 6 | (3.6) |
| Epistaxis | 4 | (1.7) | 0 | |
| Fatigue | 4 | (1.7) | 0 | |
| Hypokalemia | 4 | (1.7) | 0 | |
| Leukopenia | 4 | (1.7) | 0 | |
| Rhinitis | 4 | (1.7) | 5 | (3.0) |
| Asthma | 3 | (1.3) | 1 | (0.6) |
| Bronchitis | 3 | (1.3) | 2 | (1.2) |
| Constipation | 3 | (1.3) | 2 | (1.2) |
| Flatulence | 3 | (1.3) | 0 | |
| Hematuria | 3 | (1.3) | 1 | (0.6) |
| Hypertension | 3 | (1.3) | 3 | (1.8) |
| Injury | 3 | (1.3) | 3 | (1.8) |
| Leukocytosis | 3 | (1.3) | 1 | (0.6) |
| Pain | 3 | (1.3) | 2 | (1.2) |
| Pleural Effusion | 3 | (1.3) | 0 | |
| Vomiting | 3 | (1.3) | 5 | (3.0) |
| Dyspepsia | 2 | (0.9) | 2 | (1.2) |
| Neuralgia | 2 | (0.9) | 2 | (1.2) |
| Pneumonia | 2 | (0.9) | 2 | (1.2) |
| Respiratory Disorder | 2 | (0.9) | 4 | (2.4) |
| Chronic Obstructive Airways Disease | 1 | (0.4) | 3 | (1.8) |
| Coughing | 1 | (0.4) | 3 | (1.8) |
| Dehydration | 1 | (0.4) | 2 | (1.2) |
| Gastritis | 1 | (0.4) | 4 | (2.4) |
| Mouth Dry | 1 | (0.4) | 2 | (1.2) |
| Sleep Disorder | 1 | (0.4) | 2 | (1.2) |
| Agitation | 0 | (0.0) | 2 | (1.2) |
| Asthenia | 0 | (0.0) | 3 | (1.8) |
| Depression | 0 | (0.0) | 3 | (1.8) |
| Edema Dependent | 0 | (0.0) | 3 | (1.8) |
| Infection Fungal | 0 | (0.0) | 2 | (1.2) |
| Moniliasis | 0 | (0.0) | 4 | (2.4) |
| Myocardial Infarction | 0 | (0.0) | 2 | (1.2) |
| Otitis Media | 0 | (0.0) | 2 | (1.2) |

Source: Adapted from Applicant's Table 17.35 from NDA 21-158 18 month Safety Update

The next table provides a comparison of LFT values on therapy in patients with out of range LFTs at screening for the Combined Population. As shown, 5.1% of gemifloxacin treated patients had ALT values of >4xULN with 0.9% >8xULN in comparison to 2.8% for comparator at >4xULN and none >8xULN. Also shown in this table is that 4.8% of gemifloxacin treated patients had AST values >4xULN with 1.2% >8xULN and comparator had 3.4% at >4xULN with none >8xULN at the on therapy visit. Similar percentages of patients in both arms had alkaline phosphatase levels >2xULN (10.4% for gemifloxacin and 10.2% for comparator with only 2 comparator patients >6xULN.) In the gemifloxacin arm 4.0% of patients had bilirubin elevations >2xULN in comparison to 2.3% for comparator but only gemifloxacin patients (3) had levels above 4xULN.

Another approach to the description of the above data is the following. Approximately 7% of the gemifloxacin treated patients had elevated ALT values immediately upon entry into the study. Of these patients approximately 10% showed a further elevation of their ALT at the on-therapy visit and 5% showed a further elevation at the end of therapy visit. None of these patients demonstrated hepatocellular jaundice. In the all comparators group, about 6% of patients had elevated ALT values immediately upon entry into the study. Of these patients, approximately 7% showed a further elevation of ALT at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

Table 48. Number (%) of Patients with Liver Function Tests Within Specified Ranges at the On-Therapy Visit - Patients Out of Range at Screening (Combined Population)

| Functional Group/ Variable | Range | Treatment Group | | | |
|-------------------------------|------------|----------------------------------|--------|---------------------------|--------|
| | | Gemifloxacin 320mg qd N=1121* | | All Comparators N=783* | |
| | | n/Np ⁺ | (%) | n/Np ⁺ | (%) |
| ALT | <ULN | 101/329 | (30.7) | 69/255 | (27.1) |
| | ULN-<2xULN | 144/329 | (43.8) | 135/255 | (52.9) |
| | 2-<4xULN | 67/329 | (20.4) | 44/255 | (17.3) |
| | 4-<6xULN | 11/329 | (3.3) | 6/255 | (2.4) |
| | 6-<8xULN | 3/329 | (0.9) | 1/255 | (0.4) |
| | ≥8xULN | 3/329 | (0.9) | 0/255 | |
| AST | <ULN | 108/328 | (32.9) | 84/210 | (40.0) |
| | ULN-<2xULN | 159/328 | (48.5) | 87/210 | (41.4) |
| | 2-<4xULN | 45/328 | (13.7) | 34/210 | (16.2) |
| | 4-<6xULN | 8/328 | (2.4) | 3/210 | (1.4) |
| | 6-<8xULN | 4/328 | (1.2) | 2/210 | (1.0) |
| | ≥8xULN | 4/328 | (1.2) | 0/210 | |
| Alkaline Phosphatase | <ULN | 73/289 | (25.3) | 46/207 | (22.2) |
| | ULN-<2xULN | 186/289 | (64.4) | 140/207 | (67.6) |
| | 2-<4xULN | 28/289 | (9.7) | 19/207 | (9.2) |
| | 4-<6xULN | 2/289 | (0.7) | 0/207 | |
| | 6-<8xULN | 0/289 | | 2/207 | (1.0) |

| | | | | | |
|-----------|------------|---------|--------|---------|--------|
| | ≥8xULN | 0/289 | | 0/207 | |
| Total | <ULN | 197/272 | (72.4) | 169/219 | (77.2) |
| Bilirubin | ULN-<2xULN | 64/272 | (23.5) | 45/219 | (20.5) |
| | 2-<4xULN | 8/272 | (2.9) | 5/219 | (2.3) |
| | 4-<6xULN | 2/272 | (0.7) | 0/219 | |
| | 6-<8xULN | 1/272 | (0.4) | 0/219 | |
| | ≥8xULN | 0/272 | | 0/219 | |

Data Source: Table 206b.

* N = total number of patients with out-of-range (≥ULN) values at screening.

+ n/Np = number of patients within the specified range/number of patients evaluated for the laboratory parameter.

Source Applicant's Table 17.28 from NDA 21-158, 18-month Safety Update

Table 49 Number (%) of Patients with Liver Function Tests Within Specified Ranges at the End-of-Therapy Visit - Patients Out of Range at Screening (Combined Population)

| | | Treatment Group | | | |
|----------------------|------------|---------------------------|--------|-------------------|--------|
| Functional Group/ | | Gemifloxacin 320 mg qd | | All Comparators | |
| Variable | Range | N=1121* | | N=783* | |
| | | n/Np ⁺ | (%) | n/Np ⁺ | (%) |
| ALT | <ULN | 186/377 | (49.3) | 133/234 | (56.8) |
| | ULN-<2xULN | 150/377 | (39.8) | 79/234 | (33.8) |
| | 2-<4xULN | 33/377 | (8.8) | 19/234 | (8.1) |
| | 4-<6xULN | 7/377 | (1.9) | 3/234 | (1.3) |
| | 6-<8xULN | 1/377 | (0.3) | 0/234 | |
| | ≥8xULN | 0/377 | | 0/234 | |
| AST | <ULN | 200/339 | (59) | 124/189 | (65.6) |
| | ULN-<2xULN | 112/339 | (33) | 51/189 | (27) |
| | 2-<4xULN | 22/339 | (6.5) | 12/189 | (6.3) |
| | 4-<6xULN | 3/339 | (0.9) | 1/189 | (0.5) |
| | 6-<8xULN | 1/339 | (0.3) | 1/189 | (0.5) |
| | ≥8xULN | 1/339 | (0.3) | 0/189 | |
| Alkaline Phosphatase | <ULN | 117/305 | (38.4) | 91/205 | (44.4) |
| | ULN-<2xULN | 174/305 | (57) | 109/205 | (53.2) |
| | 2-<4xULN | 12/305 | (3.9) | 4/205 | (2) |
| | 4-<6xULN | 2/305 | (0.7) | 1/205 | (0.5) |
| | 6-<8xULN | 0/305 | | 0/205 | |
| | ≥8xULN | 0/305 | | 0/205 | |
| Total | <ULN | 214/296 | (72.3) | 178/222 | (80.2) |
| Bilirubin | ULN-<2xULN | 74/296 | (25) | 39/222 | (17.6) |
| | 2-<4xULN | 8/296 | (2.7) | 5/222 | (2.3) |
| | 4-<6xULN | 0/296 | | 0/222 | |
| | 6-<8xULN | 0/296 | | 0/222 | |
| | ≥8xULN | 0/296 | | 0/222 | |

Source Applicant's Table 17.32 from 18 mont Safety Update NDA 21-158

Specific Cases of Altered Hepatic Function

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Study 185

Study 185 was a study to evaluate the treatment of CAP in hospitalized patients. Consequently these patients were older and sicker overall than most of the populations previously studied in this submission. Similar numbers of patients were in each arm. Four patients in the gemifloxacin 320mg qd from study 185 experienced AEs associated with abnormalities of hepatic function that led to withdrawal. Another patient experienced marked elevations in bilirubin but was not withdrawn. Two additional patients who were within the normal range at screening had elevations in ALT and/or AST >3xULN either on therapy or the end of therapy. There were no withdrawals from the comparator arm for hepatic enzyme elevations, but 3 patients who were in range at screening did experience elevations in at least one LFT of >3xULN.

The cases which required withdrawal from study 185 because of LFT elevations are described below.

1-Patient 185.202.30261, a 56-year-old (yo) male. The patient had no significant clinical history. Concomitant medications included acetaminophen and sotalol hydrochloride. The patient's baseline laboratory values at screening included ALT 44 IU/L (normal range 0-48 IU/L), AST 46 IU/L (normal range 0-42 IU/L), and alkaline phosphatase 41 IU/L (normal range 20-125 IU/L). On the fourth day of study medication relevant laboratory tests results showed ALT 157 IU/L, AST 141 IU/L, alkaline phosphatase 42 IU/L. The patient was asymptomatic and received no treatment for the event. Bilirubin values were normal at all times during the study. Study medication was stopped on the fifth day of treatment, and the patient was withdrawn from the study. Laboratory tests from samples taken 2 days after cessation showed ALT levels still high at 125 IU/L, while AST levels were returning to normal at 62 IU/L and alkaline phosphatase levels increased within the normal range to 51 IU/L. The event resolved between Day 7 and Day 24 (retest showed ALT 41 IU/L, AST 28 IU/L, and alkaline phosphatase increased to 69 IU/L but still normal). The investigator considered the increase in ALT and AST to be probably related to study medication.

2-Patient 185.310.29883, a 36-yo male. The patient's medical history included asthma and spinal meningitis. Concomitant or recent medications included albuterol, amoxicillin with clavulanate, azithromycin, ceftriaxone, detropropoxyphene, acetaminophen, diphenhydramine, docusate sodium, ibuprofen, ipratropium, morphine, oxycodone HCl, oxycodone terephthalate, PPD skin test, ranitidine, and cough syrup containing codeine, guaifenesin, sorbitol, and acetaminophen. Baseline laboratory values at screening included ALT 24 IU/L (normal range 0-48 IU/L), AST 12 IU/L (normal range 0-42 IU/L), and alkaline phosphatase 115 IU/L (normal range 20-125 IU/L). Elevated liver enzymes were noted on the fifth day of study medication, and relevant laboratory tests results showed ALT 233 IU/L, AST 117 IU/L, and alkaline phosphatase 368 IU/L. The patient also had an AE of pleural effusion beginning 7 days after the start of study medication; this AE was also recorded as leading to withdrawal. Bilirubin values were normal at all times during the study. Treatment with study medication was stopped after 8 doses (including an erroneous extra dose on 1 day), and the patient was withdrawn from the study. Laboratory results taken the day of the last dose of study medication showed that the liver enzymes were decreasing (ALT 186 IU/L, AST 43 IU/L, and alkaline phosphatase 352 IU/L). Both events resolved (the increased hepatic enzymes resolved within 23 days and the pleural effusion within 5 days). The investigator considered the increase in liver enzymes to be of a suspected relationship to treatment with study medication.

3-Patient 185.357.29796, an 89-y.o. female. The patient's medical history included coronary artery disease, left ventricular diastolic dysfunction, pulmonary edema, chronic obstructive pulmonary disease, left bundle branch block, iron deficiency anemia, osteoarthritis, and dementia. She had a concurrent urinary tract infection at study start. Recent medications included acetylsalicylic acid, furosemide, acetaminophen, ferrous gluconate, potassium supplement, famotidine, cefuroxime, clarithromycin, salbutamol/ipratropium hydroxide, nitroglycerine, magnesium chloride, heparin, and dimenhydrinate (Gravol). Relevant baseline laboratory values included ALT 12 IU/L (normal reference range 0-48 IU/L), AST 13 IU/L (normal reference range 0-42 IU/L), and alkaline phosphatase 87 IU/L (normal reference range 20-125 IU/L). After 7 days of treatment with study medication, test results from a local laboratory showed that the patient's liver enzymes were elevated: ALT 91 IU/L, alkaline phosphatase 401 IU/L, and gamma-glutamyl transferase (GGT) 411 IU/L (normal reference range <35 IU/L). Treatment with study medication was then stopped, and the patient was withdrawn from the study. On Day 10 of the study, further test results from the local laboratory showed that the patient's ALT had decreased to 38 IU/L, alkaline phosphatase to 260 IU/L, and GGT to 284 IU/L). The investigator considered this event possibly related to treatment with study medication.

4-Patient 185.070.29584, a 60 yo Caucasian female without significant medical history. There were no concomitant medications noted. Her screening value for ALT was 56 IU/L (reference range 0-48), for AST was 60 IU/L (reference range 0-42), for alkaline phosphatase was 86 (reference range 20-125), and for bilirubin was 9 (reference range 0-22). Two days after taking the first dose of gemifloxacin 320 mg po qd she developed an increase in ALT to 153 and AST to 119. Alkaline phosphatase rose to 143 but bilirubin remained normal. The patient was asymptomatic and study medication was discontinued. Her LFT values returned to within reference range within 7 days. The investigator considered this as a probable relation to study medication.

Study 287

Study 287 is an ongoing open label non comparative study for treating suspected pneumococcal pneumonia with 7 or 14 days of gemifloxacin 320 mg po qd. Therefore data from this study is not included in the combined clinical population. A summary of the data available was sent to the FDA in late December, 2002. At that time 355 patients had been evaluated for safety. There were 2 cases where there were LFT elevations of ALT elevation >3xULN with BR elevations of >1.5mg/dl noted. The descriptions of these cases follow.

Subject 287.022.49638 had a medical history of diabetes mellitus. At study entry his ALT was 35 IU/L and it rose to 161.0 at the end of therapy. AST rose from 69 to 614 and total bilirubin from 12.8 to 31.6 umol/L. Other AEs which developed on study included an increased CPK, sepsis, and abnormal renal function.

Subject 287.104.60413 also had a medical history of diabetes mellitus. ALT rose from 25 IU/L on entry to 127 at the end of therapy and total bilirubin from 15 to 35 umol/L. Other treatment emergent AEs included malaise and hypokalemia.

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Additional Cases with LFT Elevations of Interest

Combined ALT and Bilirubin Elevations

In the combined clinical studies population no patient in either group who was in range at screening for ALT and total bilirubin developed an ALT >3xULN with a concomitant bilirubin (BR) of 1.5 mg/dl at the on-therapy or end of therapy visit. One comparator patient who was tested after screening only at followup had an ALT of 1186 IU/L with a BR of 2.7 mg/dl at that time. There were two patients as described above in Study 287 (which was included in the combined clinical population) with ALT elevations of ALT>3xULN with BR> 1.5mg/dl.

If the threshold is changed to an ALT of >2xULN with a BR of >1.5mg/dL there were no further patients in comparator but 3 patients in the gemifloxacin group achieving this level of abnormality. In addition there were 2 patients in the gemifloxacin group with borderline ALTs at screening (49 and 50 with an ULN of 48 IU/L) who had ALT increases to >2xULN and BR increases to >1.5 mg/dl. There were no similar borderline cases in comparator patients. Below are some examples of patients who received gemifloxacin with LFT changes of clinical concern.

1-185.305.29877 – This 35 yo Black male was treated for community acquired pneumonia (CAP) with 320 mg gemifloxacin for 14 days. He reportedly had a current history of anemia and elevated liver function tests. He was on no concomitant medications. His total eosinophil count was unremarkable. This patient's bilirubin rose to 68 µmol/L from 23.9 (0-22.2µmol/L) while receiving gemifloxacin. However, the patient's ALT at this time was 172 IU/L, which was down from 225 IU/L at screening. The ALT rose to 271 at end therapy and the bilirubin fell to 15.4 µmol/L at end therapy. The AST was 202 at screening, 128 at the on therapy visit, and 300 at end therapy.

2-009.086.09326 – This 42 yo Caucasian female was treated for ABS with 320 mg gemifloxacin po qd for 10 days. She experienced no treatment-emergent adverse events and was on no other medications. Her total eosinophil count was unremarkable. Bilirubin rose from 8 to 46 µmol/L at the end of therapy and the ALT peaked at 102 IU/L from 50 IU/L at screening.

3-012.061.17962 – This 70 yo Caucasian female was treated for an acute exacerbation of chronic bronchitis with 320 mg gemifloxacin for 4 days. Her past medical history was remarkable for a previous cholecystectomy. Concomitant and recent medications included atropine sulfate, metamizole sodium, metoclopramide, gentamicin, and cefuroxime. Other treatment-emergent adverse events included diarrhea, gastritis, and thrombocytopenia. These all resolved spontaneously. Her total eosinophil count was unremarkable. This patient's bilirubin rose from 11 to 33 µmol/L and the ALT was 123 IU/L while on therapy up from 36 IU/L at screening.

4-014.016.06936. This was a 38 yo Caucasian male with a complicated UTI treated for 10 days with gemifloxacin 320 mg. Concomitant and recent medications included acetaminophen and phenazopyridine. Other adverse events included headache and erythematous rash which led to early withdrawal. His bilirubin peaked at 46µmol/L from 17.1 with an ALT of 162 IU/L from 137 at screening. The eosinophil count was normal.

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ALT elevations only

No patients who received 320 mg doses of gemifloxacin and had normal LFT's at screening had an ALT elevation >8xULN. Three patients with out of range ALT at screening had ALT of >8xULN. One of these patients is described here.

Patient 061.043.13830 was a 32 y.o. Asian male treated for CAP with 320 mg of Gemifloxacin for 7 days. His past medical history was remarkable for an intracranial injury and seizures in 1998. Concomitant medications only included a combination prescription product that included loratadine and pseudoephedrine sulfate along with an over-the-counter cough syrup and cold remedy medication consisting of phenacetin, phenylpropanolamine, and phenyltoloxamine. He had no other adverse events. His total eosinophil count was unremarkable. This patient had a rise in ALT from 110 IU/L (~2.5X ULN) to 501 (~10 X ULN) on therapy, returning to 132 IU/L at end of therapy.

The higher level incidence of ALT elevations in patients receiving 480 and 640 mg doses of gemifloxacin was also noted. The following two patients experienced ALT elevations exceeding 8 X ULN:

Patient 067.011.17797 was a 55 y.o. Caucasian female treated for an uncomplicated UTI with a single oral 640 mg dose of gemifloxacin. Concomitant medications consisted of metoprolol succinate, spironolactone, cyproterone, and estradiol. Her total eosinophil count was unremarkable. This patient experienced an ALT elevation to 8 X ULN (374 IU/L) two days after receiving the 640 mg dose. The ALT fell to roughly 2 X ULN (72 IU/L) 6 days later, with return to normal documented approximately one month later.

Patient 067.059.17989 was a 56 y.o. female treated for an uncomplicated UTI with a single oral 640 mg dose of gemifloxacin. There were no concomitant medications. Hyperglycemia was the only other treatment-emergent adverse event. Her total eosinophil count was unremarkable. This patient experienced an ALT elevation to 10 X ULN (432 IU/L) 3 days after receiving the 640 mg dose. The ALT had fallen to ~1.5 X ULN (69 IU/L) seven days later, and no follow up value was obtained.

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CARDIOVASCULAR—VITAL SIGNS AND ECG EFFECTS

Vital Signs

Clinical Pharmacology

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Vital signs were recorded for over 1500 non-patient gemifloxacin treated subjects and over 350 subjects receiving placebo. In this combined healthy population the incidence of F2 transitions in semi-supine blood pressure was comparable and actually lower than those seen with placebo.

Table 50. Vital Signs: Changes from Baseline Considered to be of Potential Clinical Concern (F2 Transitions) in Non-Patient Subjects Receiving Gemifloxacin (All Regimens) and Placebo

| Subject session counts | | Treatment Group | |
|------------------------|------|---------------------------|--------------|
| | | Gemifloxacin All doses | Placebo |
| Semi-Supine Vital Sign | | n(%) | n(%) |
| Diastolic | High | 39/1503 (2.5)* | 27/354 (7.6) |
| | Low | 46/1503 (3.0)* | 24/354 (6.7) |
| Systolic | High | 20/1503 (1.3) | 17/354 (4.8) |
| | Low | 29/1503 (1.9) | 9/354 (2.5) |

Data Source: Data Source Table DST17
Source Table 11.2 in the Safety Update.

Clinical Studies

Table 51 on the next page will summarize the percentage of patients in the gemifloxacin treated and comparator patients who had vital signs of potential clinical concern. Overall there were very similar percentages for both groups. At the on therapy and end of therapy visit there were no greater than 2% of patients in any category who had high or low values seen in either group.

In the clinical studies post NDA population 8 patients in each of the gemifloxacin and comparator groups had blood pressure values that were associated with an AE at the on therapy, end of therapy, or follow-up visits.

Of those treated with gemifloxacin in the post-NDA studies, 3 patients had elevated systolic blood pressures of clinical concern at the on therapy visit that were associated with an AE (hypertension.) At follow-up 5 patients had increases in blood pressure (4 diastolic, 1 systolic, 1 cardiac failure). Review of the narratives of these events confirms the investigators' conclusions that none appear to be related to study medication.

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**Table 51. Number of Patients with Vital Signs of Potential Clinical Concern-
Combined Population**

| Vital Sign On-Therapy | | Treatment Group | | | |
|---|--------|------------------------------------|---------|---------------------------|---------|
| | | Gemifloxacin 320mg od N=6775 | | All Comparators N=5248 | |
| | | n/Np | (%) | n/Np | (%) |
| Systolic Blood Pressure (mmHg) | High | 82/5536 | (1.5) | 48/4190 | (1.1) |
| | Low | 2/5536 | (<0.1) | 4/4190 | (0.1) |
| | Within | 5452/5536 | (98.5) | 4138/4190 | (98.8) |
| Diastolic Blood Pressure (mmHg) | High | 81/5533 | (1.5) | 67/4190 | (1.6) |
| | Low | 3/5533 | (0.1) | 1/4190 | (<0.1) |
| | Within | 5449/5533 | (98.5) | 4122/4190 | (98.4) |
| Pulse Rate (beats/min) | High | 1/5624 | (<0.1) | 3/4269 | (0.1) |
| | Within | 5623/5624 | (100.0) | 4266/4269 | (99.9) |
| End-of-Therapy Systolic Blood Pressure (mmHg) | High | 86/5405 | (1.6) | 80/4094 | (2.0) |
| | Low | 5/5405 | (0.1) | 6/4094 | (0.1) |
| | Within | 5314/5405 | (98.3) | 4008/4094 | (97.9) |
| Diastolic Blood Pressure (mmHg) | High | 101/5402 | (1.9) | 72/4094 | (1.8) |
| | Low | 6/5402 | (0.1) | 1/4094 | (<0.1) |
| | Within | 5295/5402 | (98.0) | 4021/4094 | (98.2) |
| Pulse Rate (beats/min) | High | 1/5416 | (<0.1) | 1/4097 | (<0.1) |
| | Within | 5415/5416 | (100.0) | 4096/4097 | (100.0) |
| Follow-up Systolic Blood Pressure (mmHg) | High | 104/6100 | (1.7) | 107/4752 | (2.3) |
| | Low | 5/6100 | (0.1) | 5/4752 | (0.1) |
| | Within | 5991/6100 | (98.2) | 4640/4752 | (97.6) |
| Diastolic Blood Pressure (mmHg) | High | 125/6097 | (2.0) | 83/4752 | (1.7) |
| | Low | 6/6097 | (0.1) | 6/4752 | (0.1) |
| | Within | 5966/6097 | (97.9) | 4663/4752 | (98.1) |
| Pulse Rate (beats/min) | High | 1/6103 | (<0.1) | 1/4757 | (<0.1) |
| | Within | 6102/6103 | (100.0) | 4756/4757 | (100.0) |

Source Table 11.14 from Safety Update

Electrocardiographic Effects

The quinolone class of antibiotics have been associated with QT prolongation. Consequently this area of safety was an area of special attention for this safety review.

The analyses provided by the sponsor were performed using the corrected QT (QTc) using Bazett's formula.

Preclinical

Gemifloxacin was compared with other fluoroquinolones in in vitro and in vivo assay systems. In dog in vivo the following percentage increases in action potential duration at 90% repolarization (APD90) (1Hz) at 100um were caused by sparfloxacin (72%), grepafloxacin (37%), moxifloxacin (25%), gatifloxacin (19%), and gemifloxacin (15%). Levofloxacin only causes a 23% increase in APD90 at 1000 um.

IC50 values for inhibition of hERG expressed in a kidney cell line were: sparfloxacin (37um), grepafloxacin (93um), gemifloxacin (260um), gatifloxacin (329um), moxifloxacin (354) and levofloxacin (827 um).

Study SB-265805/RSD-100THH/1 was a single dose intravenous study in conscious beagle dogs. Dogs were dosed with 3, 10, and 30 mg/kg of gemifloxacin (as free base) or placebo.

With doses of 30 mg/kg, the QTc interval increased by about 16% (maximum increase of 44.8 msec over mean baseline of 281.3 msec). The peak increase occurred 5 minutes after the end of infusion and returned to baseline approximately 30 minutes after the end of infusion. An increase in QRS complex duration was observed in the 30 mg/kg group with a maximum increase of 24.7 msec over the mean baseline value of 58.4 msec. The increases in QRS duration occurred approximately 20 minutes after infusion and returned to baseline at 80 minutes after the end of infusion. A transient decrease in the PR interval was associated with an initial increase in heart rate observed during the first part of the infusion.

The no-effect dose for cardiovascular changes in the beagle dog in this study was 10 mg/kg, when gemifloxacin was given as an IV infusion over 30 minutes. For the 30 mg/kg dose, the Cmax for male and female dogs was 7.42 $\mu\text{g/ml}$ and 9.55 $\mu\text{g/ml}$ respectively. The AUC for the 30 mg/kg dose in male and female dogs was 22.4 $\mu\text{g-hr/ml}$ and 34.7 $\mu\text{g-hr/ml}$, respectively.

Clinical Pharmacology Studies

In the combined clinical pharmacology population ECG data was obtained in over 1800 healthy subjects who received gemifloxacin, in over 400 subjects who received placebo and in 477 receiving other study drug. Manual measurements were obtained in close to 1400 gemifloxacin treated participants, the large majority (1011) of these participants were the female subjects under the age of 40 who were enrolled in rash study 344.

The following table presents the data of F3 transitions for the combined clinical pharmacology population.

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Table 52. Clinical Pharmacology Studies Combined Population (Healthy Volunteers Only): Number (%) of Subject Sessions with ECG Measurements of Potential Clinical Concern On-Therapy (F3 Transitions)

| Subject Session Counts** | Treatment | Treatment | | |
|---|-----------|----------------------------|-----------------------|----------------------|
| | | Gemifloxacin Only n (%) | Placebo only n (%) | Other only* n (%) |
| M_QTc† >470msec (females) >450msec(males) | High | 16/1395 (1.1) | 7/415 (1.6) | 8/477 (1.6) |
| PR interval >300msec | High | 0/1706 (0.0) | 1/414 (0.2) | 0/553 (0.0) |
| QRS interval >200msec | High | 0/1873 (0.0) | 1/453 (0.2) | 0/638 (0.0) |
| QTc interval >500msec | High | 2/1853 (0.1) | 0/453 (0.0) | 0/606 (0.0) |

Data Source: Table DST22

† M_ Manually read ECG Parameter

*only subjects from the post-NDA population receiving ciprofloxacin alone had F3 transitions

**an additional 20 gemifloxacin, 10 placebo and 10 other only subject sessions from NDA Study 021 were reanalyzed manually and this information is included in this table

Source: Applicant's Table 11.5 from NDA 21-158 18 month Safety Update

Two gemifloxacin treated subjects had electronic QTc values of greater than 500 msec. One of them was a participant in study 344.

Overall the incidence of F3 transitions is similar for gemifloxacin, placebo and other treated groups. In addition the percentage of healthy volunteer subject sessions with manually measured QTc values flagged as F1, F2, and F3 transitions were again similar in gemifloxacin treated subjects and placebo: 6.8%, 3.0%, and 1.1% for gemifloxacin subjects and 10.6%, 4.0%, and 1.6% for placebo.

Mean Manual QTc changes

Study 344 subjects were evaluated in Parts A and B for changes in baseline in Manual QTc. The table below illustrates that the administration of either gemifloxacin or ciprofloxacin resulting in on average a 4.9 msec increase in manual QTc from baseline.

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Table 53. Summary of Change From Baseline in Manual QTc from Part A of Study 344

| Regimen | Comparison | n | Mean | s.d. | Median | Min | Max |
|---------------|------------|-----|------|-------|--------|------|-----|
| Gemifloxacin | Single-Pre | 831 | 1.9 | 23.07 | 2 | -121 | 76 |
| | Repeat-Pre | 788 | 4.9 | 25.10 | 4 | -88 | 105 |
| Ciprofloxacin | Single-Pre | 169 | 3.8 | 21.71 | 6 | -57 | 69 |
| | Repeat-Pre | 160 | 4.9 | 23.85 | 5 | -78 | 63 |

Source: Appendix C of report for Study 344

Source: Applicant's Table 11.8 from NDA 21-158 18 month Safety Update

Clinical Studies

Paired ECG recordings were performed in seven Phase III studies (CAP Studies 011, 049 and 185, complicated UTI Study 013, and ABECB Studies 105, 207, and 212). In the Combined Population paired ECG recordings were obtained in 436 of 6775 patients in the gemifloxacin group and 400 of 5248 patients in the all comparators group.

Demographics and Comorbid Conditions

In the combined population the distribution of age and gender were similar in the gemifloxacin and all comparators groups (Table 54).

Table 54. Frequency Distribution for Gender and Age in Patients with Paired QTc (Combined Population)

| Demographics | | Treatment Group | | | |
|------------------|----------------|--------------------------------|--------|--------------------------|--------|
| | | Gemifloxacin 320mg qd N=407 | | All Comparators N=380 | |
| | | n | (%) | n | (%) |
| Gender | Male | 228 | (56.0) | 224 | (58.9) |
| | Female | 179 | (44.0) | 156 | (41.1) |
| Age Group | ≥18 to <40 yrs | 64 | (15.7) | 57 | (15.0) |
| | ≥40 to <65 yrs | 185 | (45.5) | 167 | (43.9) |
| | ≥65 to <75 yrs | 89 | (21.9) | 97 | (25.5) |
| | ≥75 yrs | 69 | (17.0) | 59 | (15.5) |

Data source: Table 252a.

Source: Applicant's Table 11.16 from the NDA 21-158 Safety Update

There are several conditions which are known to have the potential to cause QT prolongation. These include clinically significant bradycardia, idiopathic long QT syndrome, myocardial infarction/ischemia, mitral valve prolapse, hypocalcemia, hypokalemia, hypothyroidism, hypertension, cardiomyopathy, heart failure, alcohol abuse, and head injury. In the combined population about 45% of the patients in each group had at least one comorbid condition associated with prolongation of the QT interval.

Table 55. Percentage of Patients with Paired QTc with Comorbid Conditions Known to Predispose to QT Prolongation (Combined Population)

| Conditions | Treatment Group | | | |
|---|--------------------------------|--------|--------------------------|--------|
| | Gemifloxacin 320mg qd N=407 | | All Comparators N=380 | |
| | n | (%) | n | (%) |
| Patients with at least 1 comorbid condition known to predispose to QTc prolongation | 187 | (45.9) | 168 | (44.2) |
| Hypertension | 130 | (31.9) | 103 | (27.1) |
| Ischemic Heart Disease/Angina Pectoris | 60 | (14.7) | 54 | (14.2) |
| Heart Failure | 31 | (7.6) | 21 | (5.5) |
| Myocardial Infarction | 25 | (6.1) | 11 | (2.9) |
| Hypothyroidism | 19 | (4.7) | 20 | (5.3) |
| Atrial Flutter/Fibrillation | 11 | (2.7) | 10 | (2.6) |
| Alcohol Abuse/Dependence | 9 | (2.2) | 9 | (2.4) |
| Serum Potassium Decreased | 5 | (1.2) | 2 | (0.5) |
| Injury, Intracranial | 4 | (1.0) | 0 | |
| Mitral Valve Disorder | 4 | (1.0) | 1 | (0.3) |
| Tachycardia | 3 | (0.7) | 5 | (1.3) |
| Hypertensive Heart Disease | 2 | (0.5) | 1 | (0.3) |
| Extrasystoles, Ventricular | 1 | (0.2) | 1 | (0.3) |

Source: Applicant's Table 11.18 from NDA 21-158 18 month Safety Update

Certain baseline ECG abnormalities are also associated with risk factors for QT prolongation. In the combined population 38.8% of patients in the gemifloxacin group and 35.8% of the all comparator group have such ECG abnormalities.

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Table 56. Percentage of Patients with Selected ECG Abnormalities at Off-Therapy in Patients with Paired ECG Recordings (Combined Population)

| ECG Abnormality* | Treatment Group | | | |
|---|--------------------------------|--------|--------------------------|--------|
| | Gemifloxacin 320mg qd N=436 | | All Comparators N=400 | |
| | n | (%) | n | (%) |
| Patients with at least 1 selected ECG abnormality | 169 | (38.8) | 143 | (35.8) |
| S-T Changes Nonspecific | 57 | (13.1) | 42 | (10.5) |
| T Wave Inversion | 38 | (8.7) | 37 | (9.3) |
| Right Bundle Branch Block | 24 | (5.5) | 25 | (6.3) |
| Q Wave >0.04 Seconds | 17 | (3.9) | 8 | (2.0) |
| U Wave | 14 | (3.2) | 7 | (1.8) |
| PVCs Nonspecific | 12 | (2.8) | 11 | (2.8) |
| Left Ventricular Hypertrophy | 12 | (2.8) | 4 | (1.0) |
| S-T Segment Depression | 9 | (2.1) | 7 | (1.8) |
| Left Bundle Branch Block Nonspecific | 7 | (1.6) | 8 | (2.0) |
| QT Interval Increased | 5 | (1.1) | 5 | (1.3) |
| S-T Changes Segment Elevation | 4 | (0.9) | 7 | (1.8) |
| Myocardial Infarction Anterior Old | 5 | (1.1) | 2 | (0.5) |
| T Wave Peaked | 5 | (1.1) | 4 | (1.0) |
| Digitalis Effect | 4 | (0.9) | 2 | (0.5) |
| PVCs Unifocal | 6 | (1.4) | 5 | (1.3) |
| Myocardial Infarction Inferior Old | 4 | (0.9) | 6 | (1.5) |

Source: Applicant's Table 11.20 from the NDA 21-158 18 month Safety Update

It is also known that some medications are known to prolong QT interval. In the combined population 12.5% of patients in the gemifloxacin group with paired ECG recordings and 16.1% of patients in the all comparator group with paired ECG recordings received concomitant medications known to cause QT prolongation.

Mean Changes in QTc

The mean changes in QTc for the combined population are depicted below. Treatment differences between the groups were not significant in any of the populations evaluated.

Table 57. Mean Changes in the QTc Interval from the Off-Therapy Value in Patients with Paired QTc Measurements

| Population | Treatment Group | | Treatment Difference | P value |
|---|-----------------|------------|----------------------|---------|
| | Gemifloxacin | Comparator | | |
| Combined | 2.56 | -0.39 | 2.95 | 0.08 |
| Combined subset with QT prolonging conditions | 1.52 | -1.68 | 3.20 | 0.21 |

Source: Adapted from pp. 316-318 from NDA 21-158 18 month Safety Update

The range of on-therapy changes in QTc is presented in the table below. Of note is for changes of QTc greater than 50msec there were 10 patients in the gemifloxacin group in comparison to 2 in

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the all comparator group. For those same mean QTc changes in the subset of patients in the combined population who had comorbid conditions known to predispose to QT prolongation there are 6 patients in the gemifloxacin group and 1 in the all comparator group.

Table 58. Number of Patients With Changes in QTc (Combined Population)

| Change from Off-Therapy in QTc (msec) | Treatment Group | | | |
|--|-----------------------------------|--------|--------------------------|--------|
| | Gemifloxacin 320mg qd N=407 | | All-Comparators N=380 | |
| | n | (%) | n | (%) |
| < -60 | 2 | (0.5) | 1 | (0.3) |
| ≥ -60 to < -50 | 4 | (1.0) | 7 | (1.8) |
| ≥ -50 to < -40 | 7 | (1.7) | 6 | (1.6) |
| ≥ -40 to < -30 | 24 | (5.9) | 20 | (5.3) |
| ≥ -30 to < 0 | 145 | (35.6) | 155 | (40.8) |
| ≥ 0 to < 30 | 175 | (43.0) | 159 | (41.8) |
| ≥ 30 to < 40 | 23 | (5.7) | 19 | (5.0) |
| ≥ 41 to < 50 | 17 | (4.2) | 11 | (2.9) |
| ≥ 51 to < 60 | 5 | (1.2) | 0 | |
| ≥ 60 | 5 | (1.2) | 2 | (0.5) |

Source: Applicant's Table 11.24 from NDA 21-158 18 month Safety Update

Absolute QTc Values

The number and percentage of patients in the combined population who received gemifloxacin who had absolute QTc values outside of the reference range (>450 msec, male, or >470 msec, female) was higher in the gemifloxacin group than for the all comparator group but the gemifloxacin group also had a larger percentage of patients who had off therapy QTc values that were out of range. There were 3 patients in each group who had QTc values of >500 msec off-therapy but there were 5 in the gemifloxacin group who had a QTc of >500 msec on therapy in comparison to 2 in the comparator group.

Table 59. Number of Patients with Absolute QTc Greater than Reference Range (>450 msec male, >470msec female) Combined Population

| ECG Measurement | Range | Gemifloxacin 320mg qd N=407 | | All Comparators N=380 | |
|-----------------|---------|-----------------------------------|-------|--------------------------|-------|
| | | n | (%) | n | (%) |
| QTc Off-Therapy | Outside | 29 | (7.1) | 14 | (3.7) |
| QTc On-Therapy | Outside | 34 | (8.4) | 21 | (5.5) |

Source: Applicant's Table 11.28 from NDA 21-158 18 month Safety Update

Table 60. Number of Patients with QTc >500 msec Combined Population

| ECG Measurement | Range | Gemifloxacin 320mg qd | | All-Comparators | |
|-----------------|---------|--------------------------|-------|-----------------|--------------|
| | | N=407 n | (%) | n | N=380 (%) |
| QTc Off-Therapy | Outside | 3 | (0.7) | 3 | (0.8) |
| QTc On-Therapy | Outside | 5 | (1.2) | 2 | (0.5) |

Source: Applicant's Table 11.30 from NDA 21-158 18 month Safety Update

The table below lists and describes all the patients in the combined populations for both groups who had treatment emergent QT prolongation of >60 msec or >500 msec. Those patients whose off therapy value was >500msec but whose value changed minimally or decreased were not included.

Table 61. Patients with Treatment Emergent QTc prolongation (to >500 msec from <500 msec or increase in QTc by >60 msec) Combined Population (all measurements in msec)

| Medication | Patient Number | QTc off therapy | QTc on therapy | Change in QTC | Comments |
|-----------------------------|----------------|-----------------|----------------|---------------|--|
| Gemifloxacin | 185.357.29796 | 489 | 501 | 12 | LBB, CAD, Withdrawn for increased hepatic enzymes |
| Gemifloxacin | 185.364.29739 | 450 | 505 | 55 | Hypertension, LVH, CAD |
| Gemifloxacin | 212.018.52689 | 378 | 474 | 96 | Hypertension on a thiazide(lowest K 3.8), cardiomegaly |
| Gemifloxacin | 011.158.05533 | Out of range | >500 and/or | >60 | On mianserin |
| Gemifloxacin | 011.182.25945 | In range | >500 | | Low K |
| Amoxicillin-clavulanic acid | 011.182.25943 | In range | >500 and/or | >60 | |
| levofloxacin | 212.048.53882 | 393 | 457 | 64 | Hypertension, Ischemic heart disease |

Source: Adapted from pp. 322-325 NDA 21-158 18 month Safety Update

Qualitative ECG Changes

On-therapy qualitative changes were also evaluated as these may be related to a drug effect. The incidence of any qualitative changes was very small. The total percentage of patients who had paired ECG recordings in the combined population who experienced qualitative ECG changes was 4.4% in the gemifloxacin group and 6.5% in the all comparator group. The most common finding in either group was the new presence of a U wave (1.4% for gemifloxacin and 1.0% for comparator.)

Table 62. Percentage of Patients with Paired ECGs Who had Treatment Emergent Qualitative ECG Changes (Combined Population)

| ECG Abnormality | Treatment Group | | | |
|-------------------------------|--------------------------------|--------------|--------------------------|--------------|
| | Gemifloxacin 320mg qd N=436 | | All-Comparators N=400 | |
| | n | (%) | n | (%) |
| U Wave | 6 | (1.4) | 4 | (1.0) |
| S-T Changes Nonspecific | 5 | (1.1) | 11 | (2.8) |
| T Wave Inversion | 4 | (0.9) | 5 | (1.3) |
| T Wave Peaked | 2 | (0.5) | 5 | (1.3) |
| S-T Changes Segment Elevation | 1 | (0.2) | 0 | |
| S-T Segment Depression | 1 | (0.2) | 1 | (0.3) |
| Total Patients | 19 | (4.4) | 26 | (6.5) |

Source Table 11.34 Safety Update

Clinical Conditions Associated with Arrhythmias

Syncope, cardiac arrest, sudden death, and convulsions are clinical conditions that could be surrogates for drug-induced arrhythmias. No cases of torsades de pointes were reported for either treatment group.

One of the sudden deaths in the gemifloxacin arm was a 62 yo man with ABECB with “arteriosclerosis obliterans,” and a history of AF and an MI in the past. Three days after completing therapy he experienced an unexpected cardiac arrest. Review of this case by investigators drew the conclusion that his death was due to his underlying medical conditions. The other 2 cases of sudden death in the gemifloxacin arm occurred 5 and 7 days after the last dose was administered. The 3 cases of cardiac arrest in the gemifloxacin arm all occurred no earlier than 2 weeks after the last dose of gemifloxacin was given. The gemifloxacin treated patient whose diagnosis at death was listed as “Malignant Arrhythmia” was a 75 yo man with COPD, CAD, and possibly CHF on multiple medications who on the last day of therapy (which he appeared to be failing) was described as having a malignant arrhythmia and failure.

Table 63. Number of Patients in the All-Exposed population with Syncope, Convulsions, Sudden Death, Malignant Arrhythmia, and Cardiac Arrest

| Preferred Term | Treatment Group | | | |
|-----------------------|------------------------|--------|---------------------------|-------|
| | Gemifloxacin N=7659 | | All Comparators N=5549 | |
| | n | % | n | % |
| Syncope | 10 | (0.1) | 5 | (0.1) |
| Convulsions | 1 | (<0.1) | 4 | (0.1) |
| Sudden death | 3 | (<0.1) | 0 | |
| Cardiac arrest | 7 | (0.1) | 5 | (0.1) |
| Malignant Arrhythmias | 1 | (<0.1) | 0 | |

Source Adapted from Applicant's Table 11.36 from NDA 21-158, 18-month Safety Update

LABORATORY ABNORMALITIES

The effects of gemifloxacin therapy on liver function test have been covered in a separate section. This section will concentrate on abnormalities seen in hematologic parameters, renal function lab values, hypo- and hyperglycemia, and CPK abnormalities.

Hematology Values

Very few treatment emergent hematology lab parameters were seen other than what would be expected in patients with bacterial infections such as elevated white blood cell counts and increased platelet counts. There were no notable differences in the occurrence of other treatment emergent hematology lab abnormalities such as anemia, thrombocytopenia, or neutropenia. There were 3 patients treated with gemifloxacin and 2 treated with comparator who developed on-therapy neutropenia to approximately $1.0 \times 10^9/L$.

Table 64. Number of Patients with Hematology Values Outside the F2F3 Range at the On-Therapy Visit (Combined Population)

| Hematology Variable | F2F3 Range | Treatment Group | | | |
|---------------------|------------|--------------------------------------|-------|--------------------------------|--------|
| | | Gemifloxacin 320mg od N = 6775 | | All Comparators N = 5248 | |
| | | n/N* | (%) | n/N* | (%) |
| Hemoglobin | High | 4/3952 | (0.1) | 1/3671 | (<0.1) |
| | Low | 9/3952 | (0.2) | 11/3671 | (0.3) |
| Hematocrit | High | 3/3953 | (0.1) | 1/3671 | (<0.1) |
| | Low | 11/3953 | (0.3) | 10/3671 | (0.3) |
| RBCs | High | 3/3952 | (0.1) | 1/3671 | (<0.1) |
| | Low | 3/3952 | (0.1) | 0/3671 | |
| Neutrophils | High | 20/3821 | (0.5) | 11/3607 | (0.3) |
| | Low | 19/3821 | (0.5) | 25/3607 | (0.7) |
| Platelets | High | 34/3887 | (0.9) | 24/3638 | (0.7) |
| | Low | 7/3887 | (0.2) | 9/3638 | (0.2) |

Source: Table 10.15 Safety Update

Renal Chemistry Values

Changes in renal function values were infrequent and similar in both groups in the combined population. Only 0.2% of patients in either group had a serum creatinine outside the F2F3 range at both the on therapy and end of therapy visit. Please see below.

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Table 65. Number of Patients with Renal Chemistry Values Outside the F2F3 Range at the On-Therapy Visit (Combined Population)

| | | Treatment Group | | | |
|---|------------------|-------------------------------------|--------|---------------------------|--------|
| | | Gemifloxacin 320 mg qd N=6775 | | All Comparators N=5248 | |
| Renal Clinical Chemistry Variable | | n/N* | (%) | n/N* | (%) |
| | Serum creatinine | High | 9/4352 | (0.2) | 8/3881 |
| BUN | High | 15/4356 | (0.3) | 7/3880 | (0.2) |
| Calcium | High | 2/4486 | (<0.1) | 2/4003 | (<0.1) |
| | Low | 7/4486 | (0.2) | 8/4003 | (0.2) |
| Potassium | High | 2/380 | (0.5) | 3/383 | (0.8) |
| | Low | 0/380 | | 2/383 | (0.5) |
| Sodium | High | 0/352 | | 1/356 | (0.3) |
| | Low | 1/352 | (0.3) | 2/356 | (0.6) |

Source: Table 10.35 in the Safety Update

Other Metabolic Parameters (Glucose, CPK)

Values of high and low levels of glucose were almost identical in both groups in the combined clinical population. There was a slightly higher percentage of patients with a high CPK at screening and at the on-therapy visit (1.3 and 1.1 respectively) in comparison to the all comparator group (1.2 and 1.0).

Table 66. Number of Patients with Other Metabolic Clinical Chemistry Values Outside the F3 Range at the On-Therapy Visit (Combined Population.)

| | | Treatment Group | | | |
|------------------|-------------|------------------------------------|-------|------------------------------|-------|
| | | Gemifloxacin 320mg od N=6775 | | All Comparators N=5248 | |
| | F3 Range | n/N* | (%) | n/N* | (%) |
| CPK | High | 55/4178 | (1.3) | 39/3752 | (1.0) |
| Glucose - Random | High | 261/4395 | (5.9) | 229/3923 | (5.8) |
| | Low | 3/4395 | (0.1) | 4/3923 | (0.1) |

Source: Table 10.41 Safety Update

Upon review it was noted that in the post-NDA population there were 21 of 2483 subjects who received gemifloxacin who had CPK elevations outside the F2F3 range (CPK >2.5xULN) with 10 of these being above 1000. There were 6 CPK elevations in 1457 patients outside the F2F3 range in the comparator group with only 1 greater than 1000. Further examination revealed that 10 of these CPK elevations in patients on gemifloxacin were detected in men in a non-comparative NGU Study (126). Most of the participants in such a study are younger men and it is possible that much of the CPK elevations can be explained by physical activity. With all patients from non comparative gemifloxacin studies removed the difference is less impressive with 10 F2F3 elevations on gemifloxacin versus 6 from comparators. Four of the CPK elevations

on gemifloxacin were greater than 1000 versus 1 for comparator. At least one of the subjects on gemifloxacin with a CPK rise over 1000 was also taking a cholesterol lowering agent.

In the clinical studies NDA population 27 of 3865 subjects(0.8%) who received gemifloxacin had F2F3 CPK elevations at the end of therapy visit with 4 elevations being greater than 1000. In the comparator arm there 14 of 3842 patients (0.4%) with a CPK elevation in the F2F3 range at the end of therapy also with 4 greater than 1000.

In the combined clinical population there were 90 AEs or 1.3% for elevated CPK in the gemifloxacin group versus 64 or 1.2% in the all comparators group. Of note in patients with baseline liver disease AEs of myalgia were noted in 6 (2.6%) and an elevated CPK in 5 (2.1%) in the gemifloxacin group (including some subjects from non-comparative trials) while in the all comparators arm there was 1 patient with an AE of myalgia (0.6%) and 2 with elevated CPK (1.2%).

Safety by Indication

CAP

Over 2200 CAP patients were evaluated for safety 1160 received gemifloxacin and 926 received comparator. Close to 60% of patients in either arm reported at least 1 AE. Similar AE rates were seen to that in the all combined clinical population with rash however being more reported more often in the gemifloxacin arm at a rate of 4.7% . GI symptoms and taste perversion were more common in comparator.

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Table 67. Number(%) of Patients with the Most Frequently Occurring (≥1%) Adverse Experiences in CAP Studies (Combined Population)

| Preferred Term | Treatment Group | | | |
|--------------------------------|-----------------------|--------|-----------------|--------|
| | Gemifloxacin 320mg od | | All Comparators | |
| | n | (%) | n | (%) |
| Patients with at least 1 AE | 670 | (57.8) | 562 | (60.7) |
| Diarrhea | 82 | (7.1) | 87 | (9.4) |
| Headache | 61 | (5.3) | 38 | (4.1) |
| Rash* | 55 | (4.7) | 19 | (2.1) |
| Insomnia | 46 | (4.0) | 33 | (3.6) |
| Hyperglycemia | 34 | (2.9) | 25 | (2.7) |
| Nausea | 31 | (2.7) | 38 | (4.1) |
| Abdominal Pain | 29 | (2.5) | 16 | (1.7) |
| SGPT Increased | 29 | (2.5) | 39 | (4.2) |
| Thrombocythemia | 28 | (2.4) | 25 | (2.7) |
| Vomiting | 28 | (2.4) | 28 | (3.0) |
| Anemia | 26 | (2.2) | 18 | (1.9) |
| Constipation | 26 | (2.2) | 17 | (1.8) |
| Dizziness | 24 | (2.1) | 31 | (3.3) |
| Hypokalemia | 24 | (2.1) | 17 | (1.8) |
| Rhinitis | 23 | (2.0) | 14 | (1.5) |
| SGOT Increased | 23 | (2.0) | 28 | (3.0) |
| Herpes Simplex | 22 | (1.9) | 11 | (1.2) |
| Phosphatase Alkaline Increased | 20 | (1.7) | 11 | (1.2) |
| Respiratory Disorder | 20 | (1.7) | 18 | (1.9) |
| Hepatic Enzymes Increased | 18 | (1.6) | 15 | (1.6) |
| Leukocytosis | 17 | (1.5) | 14 | (1.5) |
| Pneumonia | 17 | (1.5) | 22 | (2.4) |
| Hematuria | 16 | (1.4) | 12 | (1.3) |
| Pharyngitis | 15 | (1.3) | 11 | (1.2) |
| Pleural Effusion | 15 | (1.3) | 12 | (1.3) |
| Asthma | 14 | (1.2) | 13 | (1.4) |
| Back Pain | 14 | (1.2) | 17 | (1.8) |
| Chest Pain | 12 | (1.0) | 12 | (1.3) |
| Injury | 12 | (1.0) | 10 | (1.1) |
| Sinusitis | 12 | (1.0) | 8 | (0.9) |
| Anxiety | 11 | (0.9) | 9 | (1.0) |
| Hemoptysis | 10 | (0.9) | 11 | (1.2) |
| CPK Increased | 9 | (0.8) | 13 | (1.4) |
| Dyspnea | 9 | (0.8) | 10 | (1.1) |
| Bronchitis | 8 | (0.7) | 12 | (1.3) |
| Fever | 8 | (0.7) | 13 | (1.4) |
| Hypotension | 8 | (0.7) | 9 | (1.0) |
| Hypertension | 7 | (0.6) | 12 | (1.3) |

| | | | | |
|--------------------|---|-------|----|-------|
| Pain | 7 | (0.6) | 10 | (1.1) |
| Moniliasis | 6 | (0.5) | 12 | (1.3) |
| Vertigo | 6 | (0.5) | 10 | (1.1) |
| Asthenia | 4 | (0.3) | 9 | (1.0) |
| Moniliasis Genital | 3 | (0.3) | 10 | (1.1) |
| Taste Perversion | 3 | (0.3) | 17 | (1.8) |

Source Applicant's Table 17.6 from NDA 21-158 18 Month Safety Update

There appear to be no important differences in the incidence of F2F3 hematology values either on or at the end of therapy between the groups. On therapy there was a slightly higher incidence of low neutrophil counts in gemifloxacin group (1.1%) versus 0.6% for comparator but this difference was not apparent at the end of therapy.

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Table 68. Number(%) of Patients with Hematology Values Outside the F2F3 Range in CAP Studies (Combined Population)

| Visit/Variable | F2F3 Range | Treatment Group | | | |
|-----------------------|------------|---|-------|------------------------------------|-------|
| | | Gemifloxacin 320 mg N =1160 n/Np* | (%) | All Comparators N =926 n/Np* | (%) |
| On-Therapy | | | | | |
| Hemoglobin | High | 1/968 | (0.1) | 1/848 | (0.1) |
| | Low | 5/968 | (0.5) | 7/848 | (0.8) |
| Hematocrit | High | 1/969 | (0.1) | 1/848 | (0.1) |
| | Low | 6/969 | (0.6) | 6/848 | (0.7) |
| RBCs | High | 1/968 | (0.1) | 1/848 | (0.1) |
| | Low | 2/968 | (0.2) | 0/848 | |
| Neutrophils | High | 13/914 | (1.4) | 8/817 | (1.0) |
| | Low | 10/914 | (1.1) | 5/817 | (0.6) |
| Platelets | High | 26/955 | (2.7) | 20/846 | (2.4) |
| | Low | 3/955 | (0.3) | 4/846 | (0.5) |
| End-of-Therapy | | | | | |
| Hemoglobin | Low | 7/931 | (0.8) | 9/807 | (1.1) |
| Hematocrit | High | 1/932 | (0.1) | 0/807 | |
| | Low | 8/932 | (0.9) | 3/807 | (0.4) |
| RBCs | Low | 3/931 | (0.3) | 3/807 | (0.4) |
| Neutrophils | High | 7/875 | (0.8) | 6/778 | (0.8) |
| | Low | 8/875 | (0.9) | 7/778 | (0.9) |
| Platelets | High | 71/916 | (7.8) | 72/805 | (8.9) |
| | Low | 2/916 | (0.2) | 3/805 | (0.4) |

Source: Applicant's Table 17.8 from NDA 21-158 18 Month Safety Update

There is a slightly higher incidence of F2F3 BUN and Bilirubin elevations at the on therapy visit with gemifloxacin that is not present at end therapy. The rates of CPK elevations in the F2F3 range were similar in the 2 arms. At the on therapy visit there were 2 F2F3 low glucose levels in each arm and at end therapy one on gemifloxacin and none on comparator.

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Table 69. Number(%) of Patients with Clinical Chemistry Values Outside the F2F3 Range in CAP Studies (Combined Population)

| Visit/Variable | F2F3 Range | Treatment Group | | | |
|-----------------------|------------|--|-------|------------------------------------|-------|
| | | Gemifloxacin 320 mg N=1160 n/Np* | (%) | All Comparators N =926 n/Np* | (%) |
| On-Therapy | | | | | |
| ALT | High | 34/1092 | (3.1) | 28/890 | (3.1) |
| AST | High | 25/1091 | (2.3) | 23/890 | (2.6) |
| ALK-P | High | 12/1096 | (1.1) | 10/889 | (1.1) |
| Calcium | High | 2/1103 | (0.2) | 0/887 | |
| | Low | 2/1103 | (0.2) | 1/887 | (0.1) |
| Sodium | Low | 0/152 | | 1/162 | (0.6) |
| Total Protein | Low | 2/1096 | (0.2) | 2/890 | (0.2) |
| Albumin | Low | 9/1103 | (0.8) | 1/889 | (0.1) |
| Total Bilirubin | High | 4/1100 | (0.4) | 1/891 | (0.1) |
| BUN | High | 13/1103 | (1.2) | 5/892 | (0.6) |
| Creatinine | High | 6/1094 | (0.5) | 5/891 | (0.6) |
| CPK | High | 8/917 | (0.9) | 8/728 | (1.1) |
| End-of-Therapy | | | | | |
| ALT | High | 18/1034 | (1.7) | 28/839 | (3.3) |
| AST | High | 10/1033 | (1.0) | 5/837 | (0.6) |
| ALK-P | High | 4/1037 | (0.4) | 3/837 | (0.4) |
| Calcium | Low | 2/1049 | (0.2) | 0/837 | |
| Potassium | High | 1/159 | (0.6) | 1/156 | (0.6) |
| | Low | 2/159 | (1.3) | 0/156 | |
| Sodium | Low | 0/161 | | 2/157 | (1.3) |
| Albumin | Low | 5/1049 | (0.5) | 0/838 | |
| Total Bilirubin | High | 1/1040 | (0.1) | 2/839 | (0.2) |
| BUN | High | 6/1049 | (0.6) | 8/841 | (1.0) |
| Creatinine | High | 4/1035 | (0.4) | 4/840 | (0.5) |
| CPK | High | 6/855 | (0.7) | 2/683 | (0.3) |

Source: Applicant's Table 17.10 from NDA 21-158 18 Month Safety Update

ABECB

Rash was reported in 1.5% of the patients in the gemifloxacin arm of the AECB studies. This is lower than in the combined clinical population most likely due to the very small numbers of enrollees under the age of 40. The most common AEs in both groups were diarrhea, headache, and nausea, all of which were slightly more common in comparator. Taste perversion was again much more prominent in the comparators. There was a slightly higher incidence in AE reports of elevated CPK and myalgia in the gemifloxacin arm.

Table 70 . Number(%) of Patients with the Most Frequently Occurring (≥1%) Adverse Experiences in AECB Studies (Combined Population)

| Preferred Term | Treatment Group | | | |
|-------------------------------------|------------------------------|--------|---------------------------|--------|
| | Gemifloxacin 320mg N=2847 | | All Comparators N=2591 | |
| | n | (%) | n | (%) |
| Patients with at least 1 AE | 1195 | (42.0) | 1141 | (44.0) |
| Diarrhea | 152 | (5.3) | 159 | (6.1) |
| Headache | 107 | (3.8) | 120 | (4.6) |
| Nausea | 99 | (3.5) | 98 | (3.8) |
| Abdominal Pain | 64 | (2.2) | 56 | (2.2) |
| Rhinitis | 59 | (2.1) | 46 | (1.8) |
| Dizziness | 49 | (1.7) | 68 | (2.6) |
| Bronchitis | 47 | (1.7) | 43 | (1.7) |
| Dyspnea | 47 | (1.7) | 35 | (1.4) |
| Sinusitis | 47 | (1.7) | 43 | (1.7) |
| Injury | 44 | (1.5) | 29 | (1.1) |
| Vomiting | 44 | (1.5) | 42 | (1.6) |
| Rash* | 44 | (1.5) | 21 | (0.8) |
| Myalgia | 39 | (1.4) | 23 | (0.9) |
| CPK Increased | 38 | (1.3) | 23 | (0.9) |
| Dyspepsia | 37 | (1.3) | 46 | (1.8) |
| Chronic Obstructive Airways Disease | 33 | (1.2) | 38 | (1.5) |
| Flatulence | 32 | (1.1) | 24 | (0.9) |
| Hyperglycemia | 32 | (1.1) | 27 | (1.0) |
| Back Pain | 31 | (1.1) | 27 | (1.0) |
| Insomnia | 31 | (1.1) | 36 | (1.4) |
| Chest Pain | 27 | (0.9) | 29 | (1.1) |
| Constipation | 25 | (0.9) | 30 | (1.2) |
| Fatigue | 25 | (0.9) | 30 | (1.2) |
| Upper Respiratory Tract Infection | 25 | (0.9) | 27 | (1.0) |
| Coughing | 21 | (0.7) | 28 | (1.1) |
| Pharyngitis | 21 | (0.7) | 41 | (1.6) |
| Asthma | 18 | (0.6) | 29 | (1.1) |
| Mouth Dry | 18 | (0.6) | 32 | (1.2) |
| Taste Perversion | 7 | (0.2) | 83 | (3.2) |

Source: Applicant's Table 17.12 from NDA 21-158 18 Month Safety Update

There were no important differences in the rates of F2F3 hematology lab values between the 2 groups.

Table 71. Number(%) of Patients with Hematology Values Outside the F2F3 Range in AECB Studies (Combined Population)

| Visit/Variable | F2F3 Range | Treatment Group | | | |
|-----------------------|------------|-------------------------------------|-------|---------------------------|-------|
| | | Gemifloxacin 320 mg od N=2847 | | All Comparators N=2591 | |
| On-Therapy | | n/Np* | (%) | n/Np* | (%) |
| Hemoglobin | High | 2/1358 | (0.1) | 0/1204 | |
| | Low | 2/1358 | (0.1) | 2/1204 | (0.2) |
| Hematocrit | High | 2/1358 | (0.1) | 0/1204 | |
| | Low | 2/1358 | (0.1) | 2/1204 | (0.2) |
| RBCs | High | 2/1358 | (0.1) | 0/1204 | |
| Neutrophils | High | 2/1301 | (0.2) | 3/1192 | (0.3) |
| | Low | 2/1301 | (0.2) | 6/1192 | (0.5) |
| Platelets | High | 5/1328 | (0.4) | 0/1191 | |
| | Low | 1/1328 | (0.1) | 3/1191 | (0.3) |
| End-of-Therapy | | | | | |
| Hemoglobin | High | 1/1695 | (0.1) | 1/1548 | (0.1) |
| | Low | 1/1695 | (0.1) | 2/1548 | (0.1) |
| Hematocrit | High | 2/1696 | (0.1) | 2/1548 | (0.1) |
| | Low | 2/1696 | (0.1) | 2/1548 | (0.1) |
| RBCs | High | 1/1695 | (0.1) | 0/1548 | |
| | Low | 2/1695 | (0.1) | 2/1548 | (0.1) |
| Neutrophils | High | 20/1642 | (1.2) | 13/1533 | (0.8) |
| | Low | 6/1642 | (0.4) | 5/1533 | (0.3) |
| Platelets | High | 9/1666 | (0.5) | 8/1536 | (0.5) |
| | Low | 2/1666 | (0.1) | 2/1536 | (0.1) |

Table Applicant's Table 17.14 from NDA 21-158 18 Month Safety Update

CPK F2F3 elevations were similar in both groups. The incidence of F2F3 ALT elevations in the gemifloxacin group was slightly higher both at the on therapy and end of therapy visits.

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Table 72. Number (%) of Patients with Clinical Chemistry Values Outside the F2F3 Range in AECB Studies (Combined Population)

| Visit/Variable | F2F3 Range | Treatment Group | | | |
|-----------------------|------------|-------------------------------------|-------|---------------------------|-------|
| | | Gemifloxacin 320 mg od N=2847 | | All Comparators N=2591 | |
| On-Therapy | | n/Np* | (%) | n/Np* | (%) |
| ALT | High | 11/1536 | (0.7) | 1/1308 | (0.1) |
| AST | High | 11/1536 | (0.7) | 3/1308 | (0.2) |
| ALK-P | High | 0/1564 | | 1/1323 | (0.1) |
| Total Protein | Low | 1/1545 | (0.1) | 0/1313 | |
| Albumin | Low | 3/1566 | (0.2) | 0/1329 | |
| Total Bilirubin | High | 3/1558 | (0.2) | 0/1321 | |
| Creatinine | High | 2/1567 | (0.1) | 1/1325 | (0.1) |
| BUN | High | 0/1562 | | 1/1326 | (0.1) |
| Calcium | Low | 2/1692 | (0.1) | 1/1448 | (0.1) |
| Potassium | High | 1/97 | (1) | 1/97 | (1) |
| | Low | 0/97 | | 1/97 | (1) |
| Sodium | Low | 1/65 | (1.5) | 0/66 | |
| CPK | High | 10/1530 | (0.7) | 8/1323 | (0.6) |
| End-of-Therapy | | | | | |
| ALT | High | 9/1773 | (0.5) | 2/1548 | (0.1) |
| AST | High | 4/1773 | (0.2) | 3/1547 | (0.2) |
| ALK-P | High | 1/1797 | (0.1) | 0/1567 | |
| Total Protein | Low | 2/1782 | (0.1) | 0/1559 | |
| Albumin | Low | 2/1801 | (0.1) | 0/1574 | |
| Total Bilirubin | High | 2/1794 | (0.1) | 1/1562 | (0.1) |
| Creatinine | High | 3/1801 | (0.2) | 2/1568 | (0.1) |
| BUN | High | 5/1797 | (0.3) | 3/1571 | (0.2) |
| Calcium | Low | 1/1798 | (0.1) | 1/1575 | (0.1) |
| Potassium | High | 1/250 | (0.4) | 0/254 | |
| | Low | 1/250 | (0.4) | 1/254 | (0.4) |
| CPK | High | 10/1765 | (0.6) | 8/1561 | (0.5) |

Source: Applicant's Table 17.16 from NDA 21-158 18 Month Safety Update

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B. Adequacy of Safety Testing

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A total of 6775 patients in the clinical studies and 1878 subjects in the clinical pharmacology studies received gemifloxacin. This is a relatively large database evaluating the safety of an antimicrobial. Clearly further surveillance will be necessary to further assess the hepatic safety and CPK effects. Study 344 to further evaluate rash was an important effort that helped to establish the natural history of the rash. The clinical and histopathology results provided an unusually large amount of quality information to the FDA Advisory Committee dermatology consultants on which to determine the nature and potential consequences of rashes associated with gemifloxacin.

C. Summary of Clinical Safety Findings and Limitations of Data

The major issues present in the safety evaluation of gemifloxacin are cutaneous adverse events, hepatic effects, QTc effects and CPK issues.

Cutaneous adverse events clearly occur with greater frequency in any subset of the clinical population by age or gender and for any indication in the gemifloxacin arm in comparison to any comparator. The incidence of rash, urticaria, withdrawal due to rash, serious adverse experience and steroid usage for treatment of rash were all higher in the gemifloxacin group in the combined clinical population. In Study 344 the rash involved greater than 60% BSA in slightly over 25% of the rashes examined. Mild mucous membrane involvement was seen in approximately 6% of the rashes in Study 344. However there were no cases of SJS or TEN and the histopathology results were consistent with a mild moderate drug exanthem. The dermatology experts invited by the FDA to the Anti-Infective Advisory Committee Meeting of March 4, 2003 did not feel there was any connection to the incidence of the rash seen in the gemifloxacin trials and more concerning cutaneous adverse events. The major limitation of the data is the inability to determine what the incidence of rare more serious cutaneous adverse events will be until a larger population is exposed to the drug. Additional data will be gathered in the post-marketing period to monitor for more serious infrequent cutaneous adverse events.

The incidence of rash was higher in persons under 40 years of age, with female gender, and with treatment longer than 7 days. It was also increased in women over 40 on hormone replacement therapy. The rate of rash in women under 40 receiving more than 7 days of therapy was just over 15%. Figure 1 of this review depicts the association of age and gender with duration of therapy. The association is most impressive for women over 40 but is also seen in men under 40 and women over 40. The incidence and nature of the rash in people of color needs to be further elucidated as so few subjects in Study 344 were women of color.

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The hepatic safety of gemifloxacin was extensively reviewed. In the combined clinical population (dose 320 mg) with normal LFT's at screening, the incidence of important LFT elevations was low and there were no combined elevations of ALT and Bilirubin. Higher but still low incidences of LFT elevations were seen in patients with liver disease at baseline or with more comorbidity. The only patients with combined ALT and Bilirubin elevations after repeat dosing with gemifloxacin were 2 patients in Study 287 which was a CAP study of suspected pneumococcal pneumonia. In an uncomplicated UTI study there were 2 patients who received 640 mg with normal LFTs at baseline who had ALT elevations of $>8 \times \text{ULN}$. Consequently, there should be surveillance of individuals with liver disease who receive this drug. In such individuals repeated courses or prolonged usage could be associated with more hepatic toxicity.

Gemifloxacin's effects on cardiac repolarization are similar to the other marketed quinolones. The change in mean QTC was small, less than 3 msec in the combined population. There were five subjects with a change in QTc of >60 msec or treatment emergent prolongation of the QTc interval to longer than 500 msec.

It is unclear whether the slight increased incidence of CPK elevation in the gemifloxacin group has any clinical significance. Further surveillance in the post marketing period would be helpful to further elucidate if this poses a risk for rare but serious myositis.

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VIII. DOSING, REGIMEN, and ADMINISTRATION ISSUES

1. ABECB-320 mg po qd for 5 days
2. CAP-320 mg po qd for 7 days
3. If Cr Cl is <40 ml/min decrease the dose to 160 mg po q day
4. Usage for longer than recommended regimens may be associated with higher rates of rash in all women and men under 40 and an increase in hepatic effects in those with baseline liver disease.
5. Safety has not been established in users under the age of 18 where there is concern based on animal studies about the effects of the quinolone class on cartilage development.
6. Safety has also not been established in pregnant women.
7. Gemifloxacin's absorption can be reduced if taken within 2 hours of most antacid preparations and sucralfate must be administered 3 hours after gemifloxacin.
8. Avoid concomitant administration with other drugs which can prolong the QT interval.

IX. USE in Special Populations

A. Evaluation of the Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Sponsor provided a tabulation –see table below –of different rates of adverse events in men versus women. In addition specific analyses were provided for the incidence of rash by age, gender, duration and indication and they are presented in the discussion of rash in the safety findings section of this review. Study 344 further examined the association of gender and rash. More extensive evaluation of lab or ECG effects were not provided but could have been determined from the data base had an important difference been suspected.

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Table 73 Number (%) of Patients With the Most Frequently Occurring ($\geq 1\%$) Adverse Experiences On-Therapy Plus 30 Days Post Therapy by Gender in Clinical Studies (Gemifloxacin 320mg) Combined Population

| Preferred Term | Male=3278 | | Gender Female=3497 | |
|---|-----------|------|-----------------------|------|
| | n | (%) | n | (%) |
| Total number of patients with at least one AE | 13 | 42.4 | 1640 | 46.9 |
| Diarrhea | 169 | 5.2 | 174 | 5.0 |
| Headache | 111 | 3.4 | 193 | 5.5 |
| Nausea | 86 | 2.6 | 179 | 5.1 |
| Rash* | 78 | 2.4 | 163 | 4.7 |
| Abdominal pain | 67 | 2.0 | 90 | 2.6 |
| Creatine phosphokinase increased | 58 | 1.8 | 32 | 0.9 |
| Hyperglycemia | 56 | 1.7 | 42 | 1.2 |
| Dizziness | 55 | 1.7 | 62 | 1.8 |
| Insomnia | 52 | 1.6 | 48 | 1.4 |
| Rhinitis | 46 | 1.4 | 59 | 1.7 |
| SGPT increased | 43 | 1.3 | 24 | 0.7 |
| Injury | 41 | 1.3 | 55 | 1.6 |
| Constipation | 37 | 1.1 | 36 | 1.0 |
| Dyspnea | 37 | 1.1 | 25 | 0.7 |
| Vomiting | 36 | 1.1 | 87 | 2.5 |
| Myalgia | 36 | 1.1 | 31 | 0.9 |
| Sinusitis | 35 | 1.1 | 49 | 1.4 |
| Bronchitis | 32 | 1.0 | 32 | 0.9 |
| Back pain | 31 | 0.9 | 62 | 1.8 |
| Flatulence | 30 | 0.9 | 39 | 1.1 |
| Dyspepsia | 28 | 0.9 | 38 | 1.1 |
| Fatigue | 26 | 0.8 | 40 | 1.1 |
| Pharyngitis | 19 | 0.6 | 38 | 1.1 |
| Moniliasis genital | 4 | 0.1 | 44 | 1.3 |

Source Applicant's Table 16.5 from NDA21-158 18 Month Safety Update

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety

The Sponsor provided data on the incidence of adverse events by age as seen in the table below. Examination of how age impacted the incidence of rash was examined and that data can be found in the safety discussion of rash. The Sponsor did not provide a direct analysis of age on the incidence of laboratory transitions.

Table 74 Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences On-Therapy Plus 30 Days Post Therapy by Age in Clinical Studies (Gemifloxacin 320mg) Combined Population

| Preferred term | Age Group, years | | | | | |
|---|---------------------|------|---------------------|------|---------------|------|
| | ≥18 - <40 N=1689 | | ≥40 - <65 N=3000 | | ≥65 N=2064 | |
| | n | (%) | n | (%) | n | (%) |
| Total number of patients with at least one AE | 774 | 45.8 | 1343 | 44.8 | 906 | 43.9 |
| Rash* | 114 | 6.7 | 88 | 2.9 | 38 | 1.8 |
| Headache | 92 | 5.4 | 154 | 5.1 | 58 | 2.8 |
| Nausea | 83 | 4.9 | 170 | 3.9 | 64 | 3.1 |
| Diarrhea | 58 | 3.4 | 162 | 5.4 | 120 | 5.8 |
| Abdominal pain | 42 | 2.5 | 57 | 1.9 | 58 | 2.8 |
| Vomiting | 36 | 2.1 | 55 | 1.8 | 32 | 1.6 |
| Creatine phosphokinase increased | 35 | 2.1 | 41 | 1.4 | 13 | 0.7 |
| Injury | 32 | 1.9 | 35 | 1.2 | 29 | 1.4 |
| Dizziness | 31 | 1.8 | 54 | 1.8 | 32 | 1.6 |
| Back pain | 30 | 1.8 | 42 | 1.4 | 21 | 1.0 |
| SGPT increased | 27 | 1.6 | 26 | 0.9 | 14 | 0.7 |
| Rhinitis | 26 | 1.5 | 65 | 2.1 | 14 | 0.7 |
| Sinusitis | 24 | 1.4 | 48 | 1.6 | 11 | 0.5 |
| Insomnia | 22 | 1.3 | 44 | 1.5 | 34 | 1.6 |
| Pharyngitis | 22 | 1.3 | 28 | 0.9 | 7 | 0.3 |
| Fatigue | 20 | 1.2 | 28 | 0.9 | 18 | 0.9 |
| Infection Viral | 19 | 1.1 | 23 | 0.8 | 12 | 0.6 |
| Urticaria | 19 | 1.1 | 13 | 0.4 | 5 | 0.2 |
| Flatulence | 13 | 0.8 | 30 | 1.0 | 26 | 1.3 |
| Hyperglycemia | 13 | 0.8 | 45 | 1.5 | 40 | 1.9 |
| Upper RTI | 13 | 0.8 | 31 | 1.0 | 13 | 0.6 |
| Constipation | 11 | 0.6 | 24 | 0.8 | 38 | 1.8 |
| Dyspepsia | 11 | 0.6 | 35 | 1.2 | 20 | 1.0 |
| Myalgia | 7 | 0.4 | 39 | 1.3 | 21 | 1.0 |
| Dyspnea | 6 | 0.4 | 27 | 0.9 | 29 | 1.4 |
| Respiratory Disorder | 6 | 0.4 | 21 | 0.7 | 23 | 1.1 |
| Bronchitis | 4 | 0.2 | 32 | 1.1 | 28 | 1.4 |
| Hypokalemia | 4 | 0.2 | 13 | 0.4 | 20 | 1.0 |
| Pneumonia | 3 | 0.2 | 18 | 0.6 | 20 | 1.0 |
| Chronic Obstructive Airway Disease | 0 | 0.0 | 17 | 0.6 | 22 | 1.1 |

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Source Applicant's Table 16.3 from NDA 21-158 18 Month Safety Update

The effects of race on the incidence of adverse experiences was presented in the table below. Again no formal analysis of the effect of race on the development of laboratory transitions was provided. Since there were so few enrollees of color in Study 344 there is

limited data to determine if there will be different outcomes (such as hypo- or hyperpigmentation) of the rash in this population.

Table 75 Number (%) of Patients With the Most Frequently Occurring ($\geq 2\%$) Adverse Experiences On-Therapy Plus 30 Days Post Therapy by Race in Clinical Studies (Gemifloxacin 320mg) Combined Population

| Preferred Term | Race | | | | | | | |
|---|-----------------|-------------|----------------|-----------|-------------------|-------------|-----------------|-------------|
| | White N=5871 | | Black N=298 | | Oriental N=227 | | Other* N=379 | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Total number of patients with at least one AE | 2630 | 44.8 | 128 | 43 | 100 | 44.1 | 171 | 45.1 |
| Diarrhea | 306 | 5.2 | 19 | 6.4 | 5 | 2.2 | 13 | 3.4 |
| Headache | 256 | 4.4 | 16 | 5.4 | 6 | 2.6 | 26 | 6.9 |
| Nausea | 231 | 3.9 | 17 | 5.7 | 5 | 2.2 | 12 | 3.2 |
| Rash* | 222 | 3.8 | 4 | 1.3 | 4 | 1.8 | 11 | 2.9 |
| Abdominal pain | 131 | 2.2 | 10 | 3.4 | 10 | 4.4 | 6 | 1.6 |
| Vomiting | 103 | 1.8 | 8 | 2.7 | 0 | 0.0 | 12 | 3.2 |
| Dizziness | 101 | 1.7 | 8 | 2.7 | 1 | 0.4 | 7 | 1.8 |
| Hyperglycemia | 87 | 1.5 | 2 | 0.7 | 5 | 2.2 | 4 | 1.1 |
| Insomnia | 85 | 1.4 | 2 | 0.7 | 9 | 4.0 | 4 | 1.1 |
| Back pain | 77 | 1.3 | 4 | 1.3 | 3 | 1.3 | 9 | 2.4 |
| Creatine phosphokinase increased | 65 | 1.1 | 13 | 4.4 | 4 | 1.8 | 8 | 2.1 |
| Constipation | 58 | 1.0 | 2 | 0.7 | 4 | 1.8 | 9 | 2.4 |
| Dyspepsia | 58 | 1.0 | 4 | 1.3 | 0 | 0.0 | 4 | 1.1 |
| Arthralgia | 34 | 0.6 | 1 | 0.3 | 1 | 0.4 | 9 | 2.4 |
| Anemia | 31 | 0.5 | 7 | 2.3 | 7 | 3.1 | 7 | 1.8 |
| Thrombocythemia | 31 | 0.5 | 2 | 0.7 | 5 | 2.2 | 4 | 1.1 |
| Hematuria | 26 | 0.4 | 1 | 0.3 | 5 | 2.2 | 1 | 0.3 |

Source Applicant's Table 16.7 from NDA 21-158 18 Month Safety Update

C. Evaluation of Pediatric Program

There was no pediatric program in this product's development.

D. Comments on Data Needed in Other Populations

1. Information on the outcome of rash in people of color.
2. Incidence of rash and outcome of rash in those who receive gemifloxacin or other quinolones after a rash has developed in a prior course to gemifloxacin.
3. Individuals with hepatic impairment for the incidence of LFT elevations and CPK elevations.

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X. Conclusions and Recommendations

Gemifloxacin is a relatively well tolerated drug of the quinolone class with particular safety issues in the area of cutaneous reactions and hepatic effects. The incidence of rash in adults under the age of 40, especially women, can reach up to 15% on therapy longer than 7 days. Although this rash is usually mild to moderate it can be severe and may require steroid therapy. There have been no cases of SJS/TEN and the FDA Advisory Committee dermatology consultants did not feel there was any connection between the gemifloxacin exanthem and the occurrence of these rare but very serious cutaneous reactions. Post marketing surveillance to determine if there is any suggestion of an increased incidence of SJS/TEN is warranted. In addition post marketing investigation into the outcome and incidence in the rash in people of color will help determine whether there any occurrences of hyper- or hypopigmentation as a result of a gemifloxacin exanthem this population. As the incidence of rash increases after day 7 of therapy surveillance to evaluate whether the recommended duration of therapy is not exceeded will be important component of the post marketing program.

The incidence of elevated liver enzymes in individuals receiving gemifloxacin at a dose of 320 mg for the recommended duration was similar to the rates to the comparator agents. There were only 2 cases of combined ALT ($>3xULN$) and bilirubin ($>1.5mg/dl$) elevations in a non-comparative CAP study. There was a slight increase in the hepatic adverse events reported in individuals with baseline liver disease over comparator. However, when higher doses of gemifloxacin were administered (480 mg or 640 mg), the incidence of LFT elevations increases. Two otherwise healthy women who received a single dose of 640 mg of gemifloxacin for uncomplicated UTIs had ALT elevations $>8xULN$. Consequently it is important that there be postmarketing surveillance to evaluate whether the recommended dose and duration of therapy are complied with and to monitor for adverse events.

It is unclear at this time whether the minor increase in CPK elevations in the gemifloxacin group (0.8%) versus comparator (0.4%) has clinical relevance. Considering the potential consequences of muscle toxicity a Phase IV program to monitor CPK elevations along with LFTs will help determine if this is a signal of toxicity.

Gemifloxacin does have the potential to affect cardiac repolarization as do other quinolones. The degree of effect of the QT interval is in the range of the other marketed quinolones. Therefore a similar plan of surveillance for cases of torsades de pointes and labeling instructions not to combine administration of gemifloxacin with other potential QT prolonging drugs is recommended.

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XI. Appendix

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Appendix A

Definition of F2 and F3 Flagging Criteria for Laboratory Values

The Sponsor developed multiple flagging criteria and applied them to clinical laboratory data collected at screening, on-therapy, and at the end of therapy. These flags are defined as follows:

Out of Laboratory Normal Range (F1): This flag denotes a value above or below the normal range supplied by the specified laboratory.

Change From Baseline (F2): This flag denotes a value that increased or decreased from baseline by more than a specified amount defined by the sponsor and is referred to as the F2 flag. The associated range is referred to as the F2 range. F2 flags are applied solely on the basis of the amount of the change from a patient's baseline value, without respect to the ending value. If a patient had an abnormally high or low baseline value, they may have an *improved* on-therapy or end-of-therapy value that is F2-flagged.

Extended Normal Range (F3): This flag denotes a value that falls outside an extended normal range defined by the sponsor. This range is independent of direction of change or other values, and is outside the normal range. This flag is referred to as the F3 flag, and the associated range is referred to as the F3 range.

Combined Flagging Criteria (F2F3): This flag denotes a value that changed (increased or decreased) from baseline by more than a specified amount and also falls outside an extended normal range. It denotes values that are both F2 and F3 flagged and is referred to as the F2F3 flag.

Table B-1 and Table B-2 list the specifications for the F2 and F3 flags that identify sponsor-defined values of potential clinical concern for hematology and clinical chemistry, respectively.

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Table B-1 Hematology F2 and F3 Flagging Criteria for Phase II and Post-NDA Clinical Studies

| Laboratory Test | F2 Lower Limit | F3 Lower Limit | F2 Lower Limit | F3 Lower Limit | Normal | Standard |
|-------------------|---------------------------|------------------------|---------------------------------------|-----------------------|-----------|----------------------|
| | F2 Higher Limit* | F3 Higher Limit* | F2 Higher Limit* | F3 Higher Limit* | Range** | Units |
| Hematology | | <i>Phase II Limits</i> | <i>Post-NDA Limits</i> | | | |
| Hemoglobin | <80% of Baseline | <80% NRL | <85% of Baseline | <85% NRL | Original | g/L |
| Hematocrit | None <80% of Baseline | >105% NRH <80% NRL | >115% of Baseline <85% of Baseline | >105% NRH <85% NRL | Original | Ratio L/L |
| Red Blood Cells | None None | >105% NRH <75% NRL | >115% of Baseline <80% of Baseline | >105% NRH <75% NRL | Original | x10 ¹² /L |
| Reticulocytes | None None | >110% NRH None | >120% of Baseline None | >110% NRH None | Original | x1A/L |
| White Blood Cells | None <75% of Baseline | None <75% NRL | None None | None*** <75% NRL | Original | x10 ⁹ /L |
| Basophils | >150% of Baseline None | >150% NRH None | None None | >150% NRH None | 0 – 0.093 | x10 ⁹ /L |
| | >200% of Baseline | >200% NRH | None | >200% NRH | | |

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| | | | | | |
|-------------|-------------------|-----------|-------------------|-----------|--------------------------------|
| Eosinophils | None | None | None | None | 0 – 0.287 x10 ⁹ /L |
| | >200% of Baseline | >200% NRH | >200% of Baseline | >200% NRH | |
| Lymphocytes | <50% of Baseline | <50% NRL | None | <50% NRL | 1.3 – 3.75 x10 ⁹ /L |
| | >200% of Baseline | >150% NRH | None | >125% NRH | |
| Monocytes | None | None | None | None | 0 – 0.34 x10 ⁹ /L |
| | >200% of Baseline | >200% NRH | None | >150% NRH | |
| Neutrophils | <75% of Baseline | <80% NRL | <50% of Baseline | <80% NRL | 1.7 – 5.75 x10 ⁹ /L |
| | >150% of Baseline | >150% NRH | >150% of Baseline | >150% NRH | |
| Platelets | <75% of Baseline | <100 | <75% of Baseline | <100 | 100 - 500 x10 ⁹ /L |
| | None | >500 | >125% of Baseline | >500 | |

* NRL = Normal Range Low; NRH = Normal Range High.

** Original = The reference range was supplied by the central laboratories.

*** Reticulocyte values were F2-flagged in error for patients in study 186.

Source: Applicant's Table 10.5 from the NDA 21-058 18-Month Safety Update

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| Laboratory Test | Table B-2 Clinical Chemistry F2 and F3 Flagging Criteria for Phase II and Post-NDA Clinical Studies | | | | | Standard Units |
|---|---|------------------------------------|--|------------------------------------|----------------|----------------|
| | F2 Lower Limit F2 Higher Limit* | F3 Lower Limit F3 Higher Limit* | F2 Lower Limit F2 Higher Limit* | F3 Lower Limit F3 Higher Limit* | Normal Range** | |
| Clinical Chemistry Phase II Limits | | | Post-NDA Limits | | | |
| ALT (SGPT) | None | None | None | None | Original | IU/L |
| AST (SGOT) | >Baseline +75% NRS None | >200% NRH None | >Baseline +75% NRS None | >200% NRH None | Original | IU/L |
| Alkaline Phosphatase | >Baseline +75% NRS None | >200% NRH None | >Baseline +75% NRS None | >200% NRH None | Original | IU/L |
| Serum creatinine | >Baseline +50% NRS None | >150% NRH <50% NRL | >Baseline +75% NRS None | >200% NRH None | Original | umol/L |
| Creatine Phosphokinase | >125% of Baseline None | >150% NRH None | >125% of Baseline None | >150% NRH None | Original | IU/L |
| Blood Urea Nitrogen | >Baseline +100% NRS None | >250% NRH None | >Baseline +100% NRS None | >250% NRH None | Original | mmol/L |
| Calcium | >150% of Baseline <Baseline -50% NRS | >150% NRH <90% NRL | >150% of Baseline <Baseline -50% NRS | >150% NRH <90% NRL | Original | mmol/L |
| Total Protein | >Baseline +50% NRS None | >110% NRH <90% NRL | >Baseline +50% NRS Baseline - 50% NRS | >110% NRH <80% NRL | Original | g/L |
| Albumin | None <Baseline -50% NRS | >110% NRH <80% NRL | None <Baseline -50% NRS | None <85% NRL | 35 - 50 | g/L |
| | None | None | None | None | | |

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Table B-2 (continued) Clinical Chemistry F2 and F3 Flagging Criteria for Phase II and Post-NDA Clinical Studies

| Laboratory Test | F2 Lower Limit F2 Higher Limit* | F3 Lower Limit F3 Higher Limit* | F2 Lower Limit F2 Higher Limit* | F3 Lower Limit F3 Higher Limit* | Normal Range** | Standard Units |
|---------------------------|--|------------------------------------|--|------------------------------------|-------------------|-------------------|
| Clinical Chemistry | <i>Phase II Limits</i> | | <i>Post-NDA Limits</i> | | | |
| Total Bilirubin | None | None | None | None | Original | umol/L |
| Random Glucose | >Baseline +50% NRS None | >150% NRH <2 | >Baseline +50% NRS None | >150% NRH <50% NRL | 2 – 8 | mmol/L |
| GGT+ | None None | >8 None | None None | >150% NRH None | Original | U/L |
| LDH++ | >Baseline + 100% NRS None | >250% NRH None | >Baseline + 100% NRS None | >250% NRS None*** | Original | U/L |
| Potassium++ | >Baseline + 50% NRS <Baseline – 50% NRS | >150% NRH <3 | >Baseline + 50% NRS <Baseline – 50% NRS | None <3 | Original | mmol/L |
| Sodium++ | >Baseline + 75% NRS <Baseline – 50% NRS | >6 <95% NRL | >Baseline + 75% NRS <Baseline – 50% NRS | >6 <95% NRL | Original | mmol/L |
| | >Baseline + 50% NRS | >105% NRH | >Baseline + 50% NRS | >105% NRH | | |

Note: ALT (SGPT) = Alanine Aminotransferase; AST (SGOT) = Aspartate Aminotransferase; GGT = Gamma-Glutamyl Transferase; LDH = Lactate Dehydrogenase.

* NRS = Normal Range Span; NRL = Normal Range Low; NRH = Normal Range High.

** Original = The reference range was supplied by the central laboratories.

*** LDH values were F2-flagged in error for patients in study 186.

+ Test performed in only studies 001, 002 and 003.

++ Test performed in only studies 001, 002 and 003 and Post-NDA studies.

Source: Applicant's Table 10.6 from the NDA 21-058 18 Month Safety Update

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Appendix B

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