Gemifloxacin for the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis and Community-Acquired Pneumonia

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INTRODUCTION

Gemifloxacin mesylate (Factive®, GeneSoft) is a new, enhanced-affinity, synthetic, broad-spectrum, fluoronaphthyridine quinolone antibacterial agent indicated for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB) and community-acquired pneumonia (CAP) of mild-to-moderate severity.

Chronic Bronchitis

Chronic bronchitis is a major health problem associated with significant morbidity and mortality and affects more than 14 million individuals in the U.S. Patients are predisposed to frequent exacerbations, characterized by increased cough, increased sputum volume, purulence, and respiratory distress. On average, one to four exacerbations occur each year in these patients and account for approximately 12 million physician visits per year in the U.S.

AECB is commonly associated with pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are rare pathogens in AECB.

Antibiotic therapy has been shown to reduce the course of the exacerbation and is considered an appropriate standard of care. Although beta-lactam antibiotics are commonly prescribed agents for lower respiratory tract infections, including AECB, beta-lactamase–producing strains and macrolide-resistant strains of *H. influenzae* and *M. catarrhalis* may represent a challenge. In addition, the rising incidence of *S. pneumoniae*, which is resistant to penicillin and macrolides, has resulted in increased concern about the efficacy of these agents in managing AECB. Therefore, new agents with improved antimicrobial activity and an acceptable safety profile are warranted.

Community-Acquired Pneumonia

CAP, a common infection that results in high morbidity and mortality, is the seventh leading cause of death in the U.S. The most common bacterial pathogen implicated in CAP is *S. pneumoniae*. Other pathogens include *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, *Staphylococcus aureus*, *M. catarrhalis*, and *Legionella pneumophila*.

Because of the increasing prevalence of penicillin-resistant *S. pneumoniae*, outpatients should receive a macrolide, doxycycline (e.g., Vibramycin®, Pfizer), or a fluoroquinolone with enhanced activity against *S. pneumoniae*. Hospitalized patients should receive a fluoroquinolone alone or an extended-spectrum cephalosporin such as cefotaxime (e.g., Claforan®, Abbott) or ceftriaxone sodium (Rocephin®, Roche) plus a macrolide. With an increasing prevalence of resistant community-acquired respiratory pathogens, more potent antimicrobial agents with improved activity against *S. pneumoniae* are clearly desirable.

PHARMACOLOGY

As a class, fluoroquinolones act by preventing deoxyribonucleic acid (DNA) synthesis through inhibition of the bacterial type II topoisomerase enzymes (DNA gyrase and topoisomerase IV), enzymes that are essential for bacterial growth. Gemifloxacin possesses a dual mechanism of action: it inhibits bacterial topoisomerase IV and gyrase enzymes, resulting in interruption of bacterial DNA synthesis.

In vitro, gemifloxacin displays activity against both gram-positive and gram-negative organisms, including respiratory infection pathogens such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Gemifloxacin also inhibits the activity of atypical organisms such as *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*.

PHARMACOKINETICS

In healthy volunteers, oral gemifloxacin 320 mg results in an absolute bioavailability of approximately 71% (95% confidence interval [CI], range, 60–84%). The observed maximum serum concentration (Cmax) ranges between 0.5 and 2 hours following administration of the dose. The terminal phase elimination half-life is independent of the dose, with an overall mean of 7.4 ± 2 hours. Approximately 20% to 30% of the administered dose is excreted unchanged in the urine.

The binding of gemifloxacin to plasma proteins in vitro is low in humans (approximately 70%). Gemifloxacin is distributed extensively into the body’s tissues and fluids. Following five days of exposure to gemifloxacin, measured concentrations in the bronchoalveolar macrophages (107 ± 77 mcg/g), epithelial lining fluid (2.60 ± 1.96 mcg/ml), and bronchial mucosa (9.32 ± 5.15 mcg/g) were higher than those in the plasma (1.4 ± 0.442 mcg/ml).

Adjustments in dosage are not recommended for patients with mild, moderate, or severe hepatic impairment or with a
creatinine clearance of 40 ml/minute or greater. For patients with creatinine clearance below 40 ml/minute and for those receiving hemodialysis and continuous ambulatory peritoneal dialysis, the clinical dose of gemifloxacin should be halved (160 mg once daily).1

**DRUG INTERACTIONS**

Gemifloxacin has a low potential for cytochrome P-450 (CYP-450) enzyme-mediated, drug–drug interactions. At the steady state, gemifloxacin 320 mcg once daily did not affect the repeated dose pharmacokinetics of oral theophylline (e.g., Slo-bid®, Aventis)17 oral digoxin (Lanoxin® GlaxoSmithKline),18 or ethinyl estradiol/levonorgestrel (e.g., Triphasil®, Wyeth-Ayerst).1 Similarly, there was no pharmacodynamic effect on prothrombin time when gemifloxacin was coadministered with warfarin (Coumadin®, Bristol-Myers Squibb).19

As a result of chelation with magnesium and aluminum salts in antacids, ferrous sulfate, and sucralfate (Cara-fate®, Aventis),20 gemifloxacin should be administered either two hours or more before, or three hours or more after, the administration of antacids or ferrous sulfate. Simultaneous administration of calcium carbonate resulted in an increased AUC and C max, whereas the administration of antacids or the equivalent were excluded.21 Coadministration of gemifloxacin with a standard seven-day double-dummy, parallel group study.30

**ACUTE EXACERBATION OF CHRONIC BRONCHITIS**

**The Wilson Study (2002)**

Wilson and colleagues compared the efficacy and safety of a five-day course of gemifloxacin with a standard seven-day regimen of clarithromycin (e.g., Biaxin®, Abbott) in patients with an AECB in the Gemifloxacin Long-term Outcomes in Chronic Bronchitis Exacerbations (GLOBE) study. They also assessed the long-term clinical outcome over 26 weeks in this randomized, double-blind, double-dummy, parallel group study.31

Adult patients older than age 40 who had a history of chronic bronchitis and AECB that was characterized by increased dyspnea, cough, and sputum purulence were eligible. Patients who were receiving systemic steroids at a dose of more than 10 mg of prednisone or the equivalent were excluded. The patients were randomly selected to receive gemifloxacin 320 mg once daily for five days or clarithromycin 500 mg twice daily for seven days. The **clinical outcome** was determined according to the signs and symptoms of AECB. The **bacteriological outcome** was evaluated according to sputum cultures and Gram staining. The outcomes were assessed at the end-of-therapy visit (days 8–12), the follow-up visit at weeks two to three (days 13–24), and the follow-up visit at weeks four to five (days 25–38). The long-term phase (26 weeks) evaluated the proportion of patients who experienced no recurrences of AECB and who did not need to be hospitalized.

At enrollment, 712 patients were randomly assigned to receive treatment: 351 to gemifloxacin and 361 to clarithromycin. The long-term study included 438 patients, 214 in the gemifloxacin group and 224 in the clarithromycin group.

Clinical success rates in the clinical per-protocol population (which involved only patients who satisfied the inclusion criteria and who adhered to the study protocol) at the two-week to three-week follow-up visit were 85.4% with gemifloxacin and 84.6% with clarithromycin. The rates in the intent-to-treat population (all randomly selected patients who took one or more doses of the study medication) were 79.5% with gemifloxacin and 78.2% with clarithromycin. Results were similar at days eight to 12 and at days 25 to 38 among the groups.

At weeks four to five, the bacteriological success rates in the per-protocol population were superior for gemifloxacin than for clarithromycin (treatment difference: 19.8%; 95% CI, range, 2.2–37.5); however, no differences were found at the end of therapy or during follow-up visits at weeks two to three.

At the long-term follow-up visit, patients who were randomly assigned to receive gemifloxacin experienced fewer recurrences of AECB that warranted further antimicrobial treatment after the initial episode (71%) than patients receiving clarithromycin (58.5%) (P = .016). In contrast, fewer patients in the gemifloxacin group (2.3%) required hospitalization during the 26-week follow-up as a result of respiratory tract infection–related illnesses, compared with patients taking clarithromycin (6.3%). In this study, gemifloxacin given for five days to treat AECB was as effective as clarithromycin given for seven days.

**The Halpern Study (2002)**

On the basis of the GLOBE results, Halpern et al. conducted a cost-effectiveness analysis of gemifloxacin and

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clarithromycin. The base-case analysis was performed from the third-party payer’s perspective and included only direct medical costs. Evaluations based on the societal perspective included both medical and lost productivity costs. The therapy was considered effective if patients did not require antimicrobial treatment after resolution of the initial episode of AECB during the 26-week follow-up study.

In the gemifloxacin group, five patients (2.34%) required hospitalization at least once; in the clarithromycin group, 14 (6.25%) needed to be hospitalized (treatment difference: -3.91% in favor of gemifloxacin [95% CI, range, -7.67 to -0.13, \( P = .059 \)). Overall, seven patients (3.3%) in the gemifloxacin group needed to be admitted and 16 (7.1%) in the clarithromycin group needed to be hospitalized (treatment difference: -3.87% in favor of gemifloxacin [95% CI, range, -8.00 to 0.26, \( P = .087 \)). Patients receiving gemifloxacin spent less time away from their usual activities than patients taking clarithromycin (8.3 days versus 10.1 days, respectively).

The mean direct cost per patient taking gemifloxacin was $247; for clarithromycin, it was $374. The mean total costs (direct plus indirect) per patient were also lower for gemifloxacin ($1,413) than for clarithromycin ($1,742). It was concluded that gemifloxacin was less costly and more effective than clarithromycin from the perspective of payers (88%) and society (84%).

The Ball Study (2001)\(^{32}\)

In another double-blind, double-dummy, multinational trial, gemifloxacin was compared with trovafloxacin (Trovan®, Pfizer). Both products were given for five days in patients with AECB. Participants received one of the following regimens: gemifloxacin 320 mg orally daily, gemifloxacin-placebo, trovafloxacin-placebo, or 200 mg of trovafloxacin. Assessments were performed at enrollment, during therapy (days two to four), at the end of therapy (days seven to nine), at the follow-up visit (days 12–19), and at the long-term follow-up visit (days 26–33).

The study included 617 patients: 303 received gemifloxacin and 314 received trovafloxacin. At follow-up (per patient analysis), clinical success rates were 91.5% for the gemifloxacin group and 87.6% for the trovafloxacin group (treatment difference: 95% CI, range, -1.2 to -9).

At the end-of-therapy (per patient population), the clinical success rates were 95.3% for those taking gemifloxin and 92.9% for those taking trovafloxacin. At the long-term follow-up evaluation (per patient population), the clinical success rates were 82.4% and 76.4%, respectively. Similar results were reported for the intent-to-treat population.

At the follow-up visit, the bacteriological success rates were 86.8% for the gemifloxin group and 82.4% for the trovafloxacin group (95% CI, range, -9.4 to -18.3).

In summary, the clinical and bacteriological efficacy of a once-daily, five-day course of gemifloxin was at least as good as that of trovafloxin in the treatment of AECB.

Wilson et al. (2003)\(^{33}\)

Another randomized, open-label, controlled, multicenter study of patients with AECB was performed in a hospital setting to evaluate the clinical and bacteriological efficacy and safety of oral gemifloxin (320 mg once daily for five days) and sequential intravenous (IV) ceftriaxone (1 g once daily for a maximum of three days), followed by oral cefuroxime axetil (Cefetin®, Glaxo-SmithKline), 500 mg twice daily for a maximum of seven days. Of the 274 patients enrolled, 128 received gemifloxin and 136 received ceftriaxone/cefuroxime.

Patients were evaluated during four visits: at screening, during therapy (days two to four), at the end of therapy (days two to four after therapy), and at follow-up (21–28 days).

The clinical success rates at follow-up in the clinical per-protocol population were 86.8% for gemifloxin and 81.3% for ceftriaxone/cefuroxime (treatment difference = 5.5, 95% CI, range, -3.9 to -14.9). Similarly, clinical success rates for the intent-to-treat population were 82.6% (114/138) and 72.1% (98/136), respectively (treatment difference: 10.5; 95% CI, range, 0.7–20.4).

At the end of therapy, the bacteriological success rates were 81.3% for gemifloxin and 82.4% for ceftriaxone/cefuroxime. The median time to hospital discharge was nine days for the gemifloxin group and 11 days for the ceftriaxone/cefuroxime group (\( P = .04 \)).

In conclusion, treatment with orally administered gemifloxin was found to be equivalent to sequential IV ceftriaxone/cefuroxime axetil treatment in hospitalized patients with AECB.

Ball et al. (2001)\(^{34}\)

An open-label, noncomparative study was performed to assess the clinical and bacteriological efficacy of gemifloxin (320 mg, once daily for seven days) in lower respiratory tract infections in patients with AECB (\( n = 261 \)) and CAP (\( n = 216 \)). Patients were evaluated during four clinic visits: at screening, during therapy (days two to four), at the end of therapy (days 9–11), and at follow-up (days 21–28).

At follow-up, the clinical response rates in the intent-to-treat population were 83.1% (95% CI, range, 77.9–87.4) in
patients with AECB and 82.9% (95% CI, range, 77.0–87.5) in patients with CAP. Bacteriological success rates were 91.2% (95% CI, range, 80.0–96.7) in patients with AECB and 77.9% (95% CI, range, 66.8–86.3) in patients with CAP. Gemi-

floxacin treatment resulted in high clinical and bacteriological success rates in patients with AECB and with CAP.

In a comparison of gemifloxacin with levofloxacin, the clinical success rates were similar (88.2%–85.1%) (treatment difference: 95% CI, 3.1 [range, –4.7 to –10.7]).

**Community-Acquired Pneumonia**

**The Lode Study (2002)**

A randomized, open-label, multicenter trial was conducted to compare the efficacy and safety of oral gemifloxacin with sequential therapy with IV ceftri-

axone, followed by oral cefuroxime (with or without a macrolide) in 345 patients hospitalized with a clinical and radiological diagnosis of CAP. Subjects were randomly assigned to receive either oral gemifloxacin 320 mg once daily for seven to 17 days or IV ceftriaxone 2 g once daily for one to seven days (plus a macrolide if clinically indicated), followed by oral cefuroxime 500 mg twice daily for one to 13 days, for a total of 14 days or less.

Patient evaluations were performed at screening, during therapy (days two to four), at the end of therapy (two to four days after therapy), and at follow-up (21–28 days after therapy). Sputum samples were collected and tested for Gram staining, routine culture, and microbiological susceptibility. Blood samples were obtained for culture if they were indicated on the basis of clinical studies.

The participants were assessed clinically and bacteriologically. Clinical success rates at the follow-up visit were 92.2% (107/116) for gemifloxacin and 93.4% (113/121) for ceftriaxone/cefuroxime (treatment difference: –1.15; 95% CI, range, –7.73 to –5.43). At the end of therapy, similar success rates were reported.

Overall, 38% of patients in the ceftri-

axone/cefuroxime group received macrolides. At the follow-up visit, the bacteriological success rates were 90.6% (58/64) for gemifloxacin and 87.3% (55/63) for ceftriaxone/cefuroxime (treatment difference: 3.32; 95% CI, range, –7.57 to –14.21). The clinical suc-

cess rate in bacteremic patients at fol-

low-up was 100%.

The median time to hospital discharge was eight days in the gemifloxacin group and nine days in the ceftriaxone/cefuroxime group (hazard ratio: 0.945; 95% CI, range, 0.747–1.194). The clinical ef-

ficacy and tolerability of oral gemi-

floxacin 320 mg once daily were similar to those of ceftriaxone/cefuroxime (with or without a macrolide) in patients who were hospitalized for moderate to severe CAP.

**File et al. (2001)**

Gemifloxacin (320 mg once daily) was compared with trovafloxacin (200 mg once daily) in 571 patients with CAP in a multicenter, randomized, double-blind, parallel-group study. The duration of treatment was intended to be seven days but was extended to 14 days if patients had severe infection, if they had a confirmed or probable diagnosis of infection with an atypical pathogen, or if the investigator decided to extend treatment. In the end, two thirds of patients were treated for seven days. All participants received oral therapy in either the outpatient or the inpatient setting.

Clinical and bacteriological outcomes were evaluated at the end of therapy (two and four days after therapy) and at follow-up (days 14–21). In the clinical per patient population, the success rates were 95.8% for the gemifloxacin group and 93.6% for the trovafloxacin group (treatment difference: 2.2%; 95% CI, range, –1.8 to –6.3). Treatment with gemifloxacin resulted in a 94% eradica-

tion of the initial pathogens, of which 100% of *S. pneumoniae* isolates were eliminated. One bacteremic isolate of *S. pneumoniae* was associated with clinical failure in the trovafloxacin group (the MIC of trovafloxacin is 8 mg/liter). Gemifloxacin was well tolerated, and the incidence of transient liver-function abnormalities was very low. Gemi-

floxacin was effective and well tolerated in patients with CAP.

**Manufacturer’s Data**

In a study of gemifloxacin and an oral amoxicillin/clavulanate regimen in patients with CAP, the clinical success rates were 88.7% for gemifloxacin and 87.6% for amoxicillin/clavulanate (treatment difference: 95% CI, 1.1 [range, –7.3 to –9.5]).

**SAFETY**

In clinical trials, treatment with gemi-

floxacin was discontinued because of adverse drug effects (ADEs) in 2.2% of patients; rash occurred in 0.9%, nausea in 0.3%, diarrhea in 0.3%, urticaria in 0.3%, and vomiting in 0.2%. In one of the studies by Wilson et al., the most frequently reported ADEs were diarrhea in 18 patients (5.1%) and nausea in 15 patients (4.3%). In the File efficacy and safety study, the most common ADEs were gastrointestinal disturbances, which affected 10.5% of the patients taking gemifloxacin. Diarrhea was reported by 2.3% of patients, and the most commonly reported severe ADEs were dyspnea in three patients and headache in two patients.

In clinical trials, the frequency of rash ranged from 0.9% to 9.1%. In addition, 5.3% of patients treated with gemifloxacin experienced central nervous system side effects. In the other Wilson study, electrocardiograms in 19 patients who received gemifloxacin showed no changes in the corrected QT (QTc) interval outside the normal range.

**CONCLUSION**

Gemifloxacin is a fluoroquinolone anti-

biotic that has recently been approved for the treatment of AECB and CAP. It exerts unique bactericidal effects by preventing the synthesis of DNA through inhibition of bacterial DNA gyrase and topoiso-

merase IV. In clinical trials, success rates in eradicating pathogens ranged from 85% to 90% for both AECB and CAP.

Administered at an oral dose of 320 mg daily, gemifloxacin was clinically comparable to clarithromycin, amoxicillin/clavulanate, IV ceftriaxone/oral cefuroxime, trovafloxacin, and levo-

floxacin. It was also more cost-effective than clarithromycin in patients with AECB.
Gemifloxacin shows activity in vitro and in vivo against penicillin-resistant, macrolide-resistant, and quinolone-resistant strains of S. pneumoniae. To prevent the development of resistance, gemifloxacin should be reserved for patients with drug-resistant S. pneumoniae infection.

REFERENCES