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Gemifloxacin

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Contents

Abstract

▲ Gemifloxacin is a fluoroquinolone antibacterial agent which has an enhanced affinity for topoisomerase IV. It has potent activity against most Gram-positive bacteria, particularly *Streptococcus pneumoniae*. Gemifloxacin is over 30-fold more active than ciprofloxacin and 4- to 8-fold more active than moxifloxacin against this pathogen.

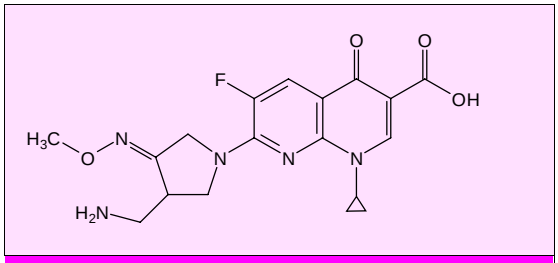
▲ Gemifloxacin has excellent activity against *Haemophilus influenzae* and *Moraxella catarrhalis*, and is unaffected by β-lactamase production. It is generally 2-fold less active than ciprofloxacin against most Enterobacteriaceae.

▲ Atypical respiratory pathogens (*Legionella*, *Mycoplasma* and *Chlamydia* spp.) are highly susceptible to gemifloxacin.

▲ Preliminary results from phase II trials show that oral gemifloxacin 320 mg/day produced bacteriological responses of 94.7% in patients with acute exacerbations of chronic bronchitis and 95% of patients with uncomplicated urinary tract infections.

▲ Adverse events included nausea, abdominal pain, headache and mild rash in patients and healthy volunteers treated with gemifloxacin 320 mg/day. Gemifloxacin has a low potential for mild phototoxicity (comparable to that of ciprofloxacin).

Features and properties of gemifloxacin (SB 265805)	
Indications	
Bacterial infections	Preregistration in US and Canada
Mechanism of action	
Fluoroquinolone antibacterial agent	Bacterial DNA gyrase and topoisomerase inhibitor
Dosage and administration	
Usual dosage in clinical trials	320mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (320mg single oral dose)	
Peak plasma concentration	1.48 mg/L
Time to peak plasma concentration	1h
Area under the plasma concentration-time curve	9.30 mg/L • h
Renal clearance	9.06 L/h
Elimination half-life	6.65h
Adverse events	
Most frequent	Nausea, abdominal pain, headache, rash



Gemifloxacin

Gemifloxacin, the focus of this profile, is a quinolone antibacterial agent which possesses an enhanced affinity for topoisomerase IV. It is a fluoronaphthyridone with a pyrrolidine substituent at C7. Gemifloxacin has an improved spectrum of antibacterial activity compared with earlier quinolones, notably against Gram-positive bacteria.[1,2]

1. Antibacterial Activity

Mechanism of Action

• Fluoroquinolones inhibit growth of bacteria by inhibiting bacterial DNA gyrase and/or DNA topoisomerase IV. The topological state of DNA is controlled by DNA gyrase, which separates and rejoins DNA strands. However, at high concentrations, some fluoroquinolones may stimulate DNA cleavage in the genomes of treated eukaryotic cells and convert type II topoisomerase into a cellular toxin.[3]

• At concentrations up to 10 000 mg/L, gemifloxacin did not cause topoisomerase II-associated DNA cleavage. In contrast, ciprofloxacin induced cleavage at a concentration of 644 mg/L. Gemifloxacin selectivity was >909.1 for bacterial DNA gyrase versus human topoisomerase II; ciprofloxacin selectivity was 7.7.[3]

• In *Streptococcus pneumoniae*, gemifloxacin IC_{50} (the concentration required to inhibit enzyme activity by 50%) values for DNA gyrase were 10-fold greater than those for topoisomerase IV (47.5 *vs* 1.4 mg/L), indicating that topoisomerase IV is the primary target in these bacteria.[4] The IC_{50} of gemifloxacin for topoisomerase IV from 3 strains of *S. pneumoniae* (2 ciprofloxacin-resistant and 1 ciprofloxacin-sensitive) was approximately 5-fold less than that for ciprofloxacin (1.4 *vs* 6.4 mg/L, respectively), indicating an enhanced affinity of gemifloxacin for topoisomerase IV.[4]

In Vitro Activity

In this profile, *in vitro* antibacterial activity refers to minimum inhibitory concentrations (MICs) determined by broth or agar dilution techniques (except in the case of some intracellular bacteria, which were tested in cell culture). MIC_{50} and MIC_{90} refer to minimum concentrations required to inhibit the growth of 50 and 90% of strains, respectively. Tentative MIC susceptibility breakpoints for gemifloxacin have been proposed: ≤0.5 and ≥2 mg/L for susceptibility and resistance, respectively.[5] The *in vitro* activity of gemifloxacin against Gram-positive and Gram-negative bacteria is presented in figures 1 and 2.

Gram-Positive Bacteria

Streptococci

• Against 300 isolates of *S. pneumoniae*, gemifloxacin was over 30-fold more active than ciprofloxacin (MIC_{90} 0.06 *vs* 2 mg/L).[9] Data from 2 studies (n = 100 and 301 isolates)[10,11] showed gemifloxacin (MIC_{90} 0.03 and 0.06 mg/L, respectively) to be 4- to 8-fold more active than moxifloxacin (MIC_{90} 0.25 mg/L)[11] and 8- to 16-fold more active than sparfloxacin (MIC_{90} 0.5 mg/L)[11] against *S. pneumoniae*. Gemifloxacin was 32-fold more active against *S. pneumoniae* than levofloxacin (MIC_{90} 1 mg/L).[10]

• The activity of gemifloxacin against *S. pneumoniae* is unaffected by penicillin resistance (MIC_{90} 0.015 to 0.032 mg/L for resistant and susceptible strains; fig. 1).[6,8] Gemifloxacin showed superior activity compared with ciprofloxacin against penicillin-resistant and penicillin-intermediate strains of *S. pneumoniae* (MIC_{90} 0.015 to 0.06 mg/L *vs* 1 to 8 mg/L, respectively).[6,10,12] Gemifloxacin was 2- to 8-fold more active than moxifloxacin,[10,12] 16- to 64-fold more active than levofloxacin and 8- to 32-fold more active than sparfloxacin against penicillin-resistant and penicillin-intermediate *S. pneumoniae*.[6,10,12]

• Studies of erythromycin-resistant *S. pneumoniae* (n = 34 and 14)[8,10] showed that gemifloxacin (MIC_{90} 0.03 mg/L) was 32- to 64-fold more active than ciprofloxacin (fig. 1), 32-fold more active than

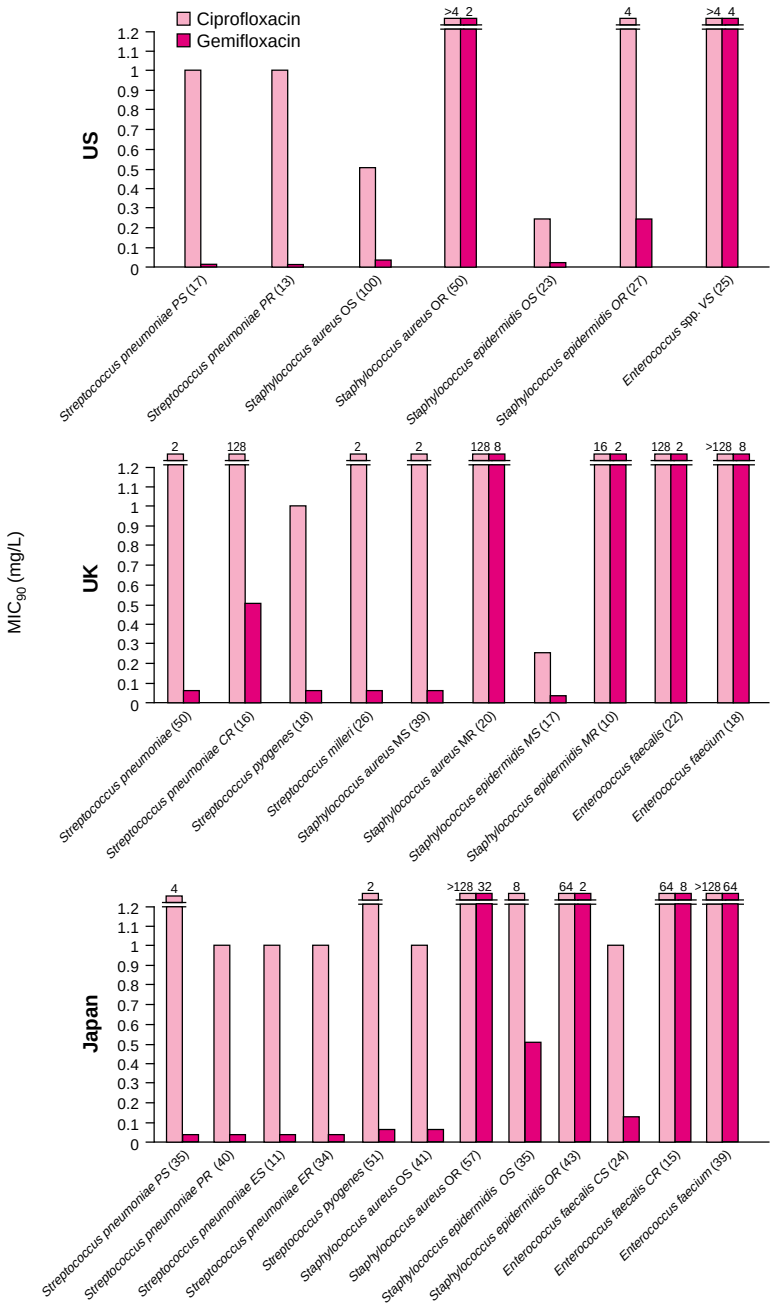


Fig. 1. *In vitro* activity of gemifloxacin and ciprofloxacin against Gram-positive bacteria from the US, UK and Japan.[6-8] **MIC_{90}** = minimum concentration required to inhibit 90% of strains; where these values are off the scale they are shown above the relevant bar; **CR** = ciprofloxacin-resistant; **CS** = ciprofloxacin-susceptible; **ER** = erythromycin-resistant; **ES** = erythromycin-susceptible; **MR** = methicillin-resistant; **MS** = methicillin-sensitive; **OR** = oxacillin-resistant; **OS** = oxacillin-susceptible; **PR** = penicillin-resistant; **PS** = penicillin-susceptible; **VS** = vancomycin-susceptible.

levofloxacin, 8-fold more active than sparfloxacin[8,10] and 8-fold more active than moxifloxacin.[10]

• In a UK study, gemifloxacin maintained good activity against ciprofloxacin-resistant strains of *S. pneumoniae* (MIC_{90} 0.5 *vs* 128 mg/L, respectively).[7] Against 28 ciprofloxacin-resistant (MIC ≥8 mg/L) pneumococcal strains, gemifloxacin had an MIC_{90} of 0.5 mg/L.[13] Gemifloxacin was >64-fold more active than levofloxacin and ciprofloxacin and 32-fold more active than sparfloxacin against these strains.[13] In a Canadian study involving 75 ciprofloxacin-resistant (MIC ≥4 mg/L) isolates of *S. pneumoniae*, gemifloxacin inhibited 95% of isolates at 0.5 mg/L; at the same concentration, moxifloxacin and gatifloxacin inhibited 63 and 59% of isolates, respectively.[14] Gemifloxacin also displayed an MIC of 0.5 mg/L against a trovafloxacin-resistant strain of *S. pneumoniae* (MIC 4 mg/L) carrying a double mutation in both *parC* and *gyrA* genes.[15]

• Gemifloxacin was 4-fold more active than moxifloxacin against 18 strains of *S. pneumoniae* with an efflux-mediated reduced susceptibility to ciprofloxacin (MIC ≥2 mg/L; norfloxacin MIC reduced ≥4-fold by reserpine).[16]

• MIC_{90} values of gemifloxacin and ciprofloxacin were 0.06 and ≥1 mg/L, respectively, for *S. pyogenes* in studies conducted in Japan[8] the UK (fig. 1),[7] and Korea.[17]

Staphylococci

• Against methicillin-susceptible (MS) strains of *Staphylococcus aureus*, gemifloxacin was 16- to 32-fold more active than ciprofloxacin (MIC_{90} 0.125 to 0.3 mg/L *vs* 1 to 2 mg/L, respectively; n = 42 and 85).[18,19] Gemifloxacin was also 16- to 64-fold more active than ciprofloxacin against MS *S. epidermidis* (MIC_{90} 0.125 to 0.3 mg/L *vs* 0.5 to 8 mg/L, respectively; n = 22 and 26)[18,19] and was 4-fold more active than moxifloxacin against both MS *S. aureus* and *S. epidermidis*.[18]

• Gemifloxacin was >2- to 16-fold more active than ciprofloxacin against methicillin-resistant (MR) *S. aureus* (MIC_{90} 4 to 8 mg/L *vs* >16 to 64 mg/L, respectively; n = 49 and 43).[18,19] Against MR *S. epidermidis*, gemifloxacin was >8- to 64-fold more active than ciprofloxacin (MIC_{90} 1 to 2 mg/L *vs* >16 to 64 mg/L, respectively; n = 32 and 17). Moxifloxacin was 2-fold less active than gemifloxacin against MR *S. epidermidis* but was 2-fold more active against MR *S. aureus*.[18]

Other Gram-Positive Bacteria

• In a study conducted in Spain, gemifloxacin demonstrated good activity (MIC_{90} 0.125 mg/L) against 15 isolates of *Listeria monocytogenes*. The corresponding MIC_{90} value for ciprofloxacin was 2 mg/L.[20]

• Gemifloxacin showed poor activity against enterococci (fig. 1).[6-8]

Gram-Negative Bacteria

• In studies conducted in the US, UK and Japan, gemifloxacin showed excellent activity against *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC_{90} ≤0.015 and ≤0.032 mg/L, respectively) [fig. 2].[6-8] The activity of gemifloxacin against both pathogens was unaffected by β-lactamase production (MIC_{90} ≤0.03 mg/L).[21,22] Gemifloxacin was 4-fold more active than ciprofloxacin against ampicillin-resistant strains of *H. influenzae* (MIC_{90} of 0.004 and 0.016 mg/L, respectively).[23]

• When tested against 26 *H. parainfluenzae* isolates, gemifloxacin inhibited 50 and 90% of strains at 0.016 and 0.03 mg/L, respectively. In comparison, both MIC_{50} and MIC_{90} values for ciprofloxacin were 0.03 mg/L.[24]

• Gemifloxacin inhibited most Enterobacteriaceae, with MIC_{90} ≤1 mg/L (fig. 2), with the exception of some Japanese and US isolates of *Citrobacter freundii* and *Providencia* spp., and some Japanese isolates of *Klebsiella oxytoca* which had higher MIC_{90} values.[6-8] Ciprofloxacin was generally 2-fold more active (range 1-fold less to 8-fold more active) than gemifloxacin against these pathogens.[6-8] Activity against *Escherichia coli* was comparable between gemifloxacin and ciprofloxacin.[6-8] Predictably, MIC_{90} values for gemifloxacin were increased against ciprofloxacin-resistant strains of Enterobacteriaceae.[6,8]

• Against *Acinetobacter baumannii*, gemifloxacin was less active than gatifloxacin (MIC_{90} 16 *vs* 8 mg/L; n = 47) but more active than ciprofloxacin (MIC_{90} >128 mg/L).[25] In a US study, gemifloxacin was 8-fold more active than ciprofloxacin (MIC_{90} 0.06 *vs* 0.05 mg/L) against *Acinetobacter*

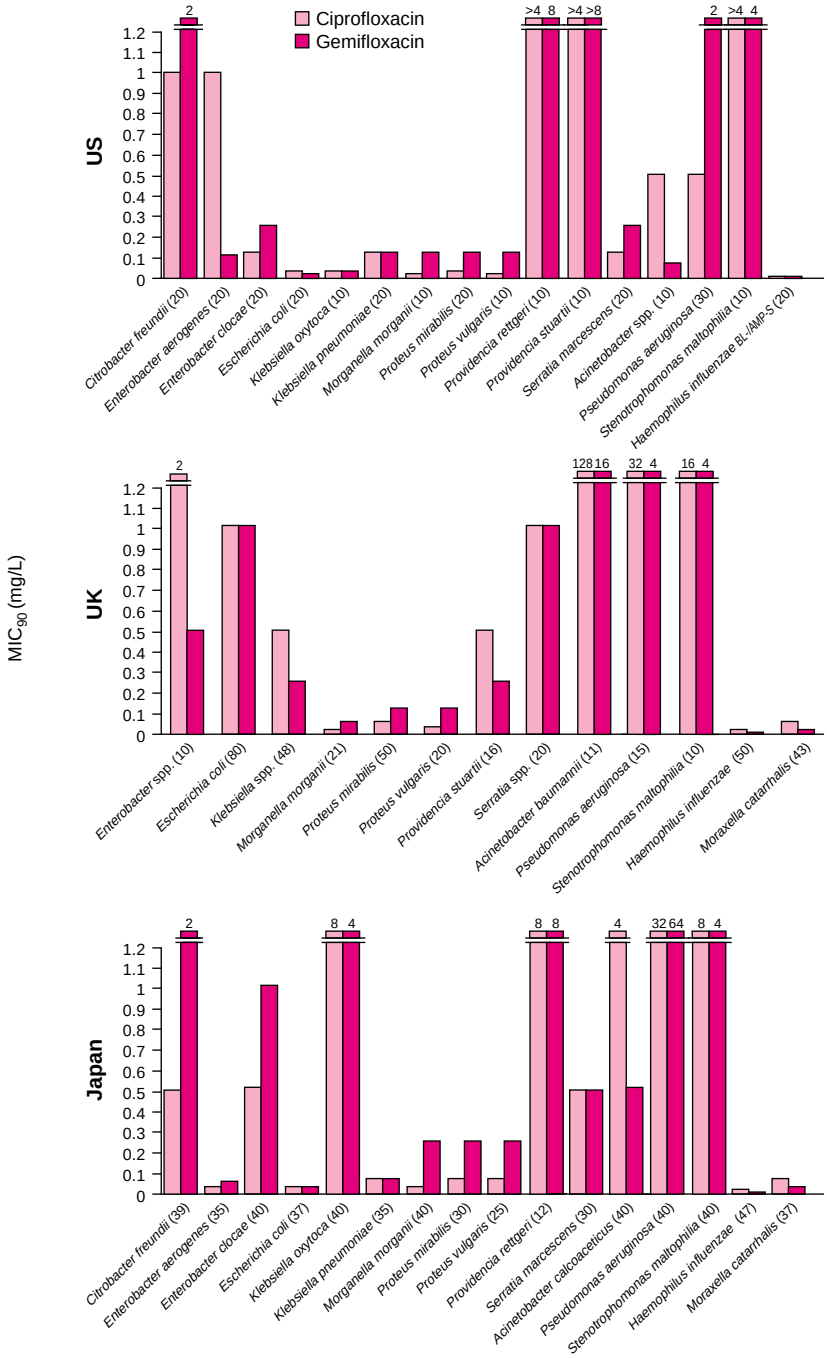


Fig. 2. *In vitro* activity of gemifloxacin and ciprofloxacin against Gram-negative pathogens (>10 isolates/group) from the US, UK and Japan.[6-8] **MIC90** = minimum concentration required to inhibit 90% of strains determined by broth or agar dilution techniques; where these values are off the scale they are shown above the relevant bar; **AMP-S** = ampicillin MIC ≤8 mg/L; **BL**- = β-lactamase negative.

spp.,[6] although in a European study a 4-fold difference was seen (MIC_{90} 1 *vs* 4 mg/L) [fig. 2].[26]

• A UK study showed that gemifloxacin was >8-fold more active than ciprofloxacin against *Pseudomonas aeruginosa*,[8] although in a US study gemifloxacin was 4-fold less active than ciprofloxacin against this species (fig. 2).[6]

Atypical Pathogens

• *Legionella* spp. (n = 238) were highly susceptible to gemifloxacin, with MICs ranging from 0.008 to 0.06 mg/L. Against *L. pneumophila* (serogroups 1 to 6), gemifloxacin (MIC_{90} 0.016 to 0.03 mg/L) showed similar activity to moxifloxacin (MIC_{90} 0.016 mg/L), levofloxacin (MIC_{90} 0.008 to 0.016 mg/L), ofloxacin (MIC_{90} 0.03 mg/L) and ciprofloxacin (0.016 to 0.06 mg/L).[27]

• Gemifloxacin was more active than ciprofloxacin against UK and US isolates of *Mycoplasma pneumoniae* and other *Mycoplasma* spp. (MIC_{90} 0.0025 to 0.1 *vs* 0.1 to 5 mg/L, respectively) as well as *Ureaplasma urealyticum* (0.25 *vs* 2.5 mg/L, respectively).[28] In particular, gemifloxacin was 5- and 10-fold more active than levofloxacin and ciprofloxacin, respectively, against *M. pneumoniae*.[28]

• Compared to both moxifloxacin and levofloxacin, gemifloxacin had 4-fold better activity against 20 isolates of *Chlamydia pneumoniae* (MIC_{90} 0.25 *vs* 1 mg/L for both comparators).[29]

Anaerobes

• Gemifloxacin showed good activity against some Gram-positive anaerobes including *Clostridium perfringens* (MIC_{90} 0.06 mg/L; n = 13) and *Peptostreptococcus* spp. (MIC_{90} 0.03 to 0.25 mg/L; n = 66).[30] In comparison, levofloxacin and sparfloxacin were 16- and 4-fold less active than gemifloxacin, respectively, against *C. perfringens*.[30] Against *Peptostreptococcus* spp. gemifloxacin was 8- to 128-fold more active than levofloxacin and 8- to 32-fold more active than sparfloxacin.[30]

• Variable activity was shown by gemifloxacin against Gram-negative anaerobes including *Bacteroides* spp. (n = 113; MIC_{90} 0.5 to >16 mg/L) and *Fusobacterium* spp. (n = 48; MIC_{90} 0.25 to 2 mg/L). MIC_{90} values for gemifloxacin were comparable to or >4-fold lower than values for levofloxacin or sparfloxacin against *Bacteroides* spp.; however, gemifloxacin was more active than levofloxacin (2- to >16-fold) and sparfloxacin (4- to 16-fold) against *Fusobacterium* spp.[30]

Bactericidal Activity

• Minimum bactericidal concentrations (MBCs) of gemifloxacin were within 1 dilution of MIC values against *S. aureus*, *E. coli*[31] and respiratory tract pathogens including *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *S. pyogenes*.[32] Time-kill studies showed that gemifloxacin achieved sustained bactericidal activity [decrease of $>3 \log_{10}$ colony-forming units (cfu)/ml] against the same pathogens at 1 to 2 × MIC. For *P. aeruginosa*, the MBC (1 mg/L) was 4-fold greater than the MIC and was required for sustained bactericidal activity.[31]

• Gemifloxacin showed greater bactericidal activity than moxifloxacin against a ciprofloxacin-resistant strain of *S. pneumoniae*; gemifloxacin reduced the viable bacterial count by $\geq 2 \log_{10}$ cfu/ml at a concentration of approximately 0.2 mg/L versus 10 mg/L with moxifloxacin (values estimated from graph).[33]

Postantibiotic Effect

• At 4 × MIC, gemifloxacin showed a postantibiotic effect (PAE) of 0.1 to >6 hours against *S. aureus*, *M. catarrhalis*, *H. influenzae*, *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *Proteus vulgaris*.[34] PAE at 4 × MIC was 1.5 and 2.7 hours against *S. pneumoniae*.[34,35] In another study in *S. pneumoniae*, the PAE was extended to 3.8 hours at 10 × MIC for both penicillin-susceptible and penicillin-resistant strains.[35]

Development of Resistance

• Spontaneous resistance to gemifloxacin (4 × MIC) was detected at a rate of $<1.1 \times 10^{\leq 9}$ to $<9.0 \times 10^{\leq 8}$ in a range of bacteria (*S. aureus*, *S. saprophyticus*, *S. pyogenes*, *S. pneumoniae*, *M. catarrhalis*, *H. influenzae*, *E. coli* and *P. aeruginosa*), with the exception of *K. pneumoniae* which showed a slightly higher rate ($4.6 \times 10^{\leq 7}$).[36] On continuous exposure to subinhibitory concentrations of gemifloxacin (0.5 × MIC), MICs increased for all bacteria except *S. saprophyticus*. However, only the MICs of *P. aeruginosa* and *K. pneumoniae* exceeded 2 mg/L after 15 passages.[36]

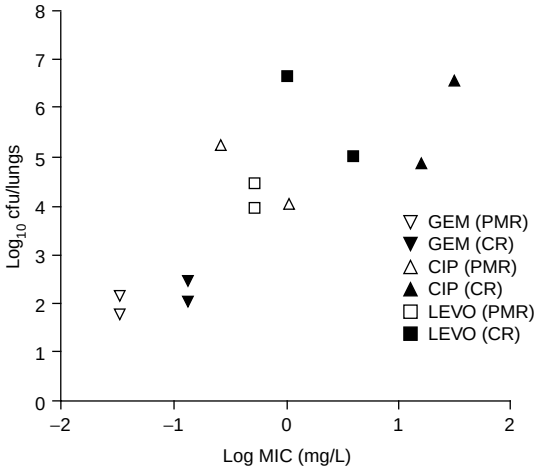


Fig. 3. Effects of gemifloxacin (GEM), ciprofloxacin (CIP) and levofloxacin (LEVO) on pneumococcal numbers in a rat model of respiratory tract infection versus minimum inhibitory concentration (MIC). Two strains each of penicillin- and macrolide-resistant (PMR) and ciprofloxacin-resistant (CR) *Streptococcus pneumoniae* were used in the study.[37,38]

In Vivo Activity

• In experimental lung infections in rats, oral gemifloxacin (240 mg/kg/day) initiated 24 hours postinfection significantly reduced bacterial counts of penicillin- and macrolide-susceptible *S. pneumoniae* 1629 to ≤1.7 $\log_{10}$ cfu/lungs compared with controls (6.8 $\log_{10}$ cfu/lungs; $p < 0.01$). In the same model, counts of 2 penicillin- and macrolide-resistant strains of *S. pneumoniae* were significantly reduced to 1.8 and 2.2 $\log_{10}$ cfu/lungs, respectively, compared with controls (5.8 and 5.0 $\log_{10}$ cfu/lungs, respectively; $p < 0.01$).[38] In animals infected with ciprofloxacin-resistant *S. pneumoniae* ($n = 2$), oral gemifloxacin initiated 1 hour postinfection and continued for 3 days significantly reduced bacterial counts to 2.4 and 2.1 $\log_{10}$ cfu/lungs, respectively, compared with controls (6.4 and 7.1 $\log_{10}$ cfu/lungs, respectively; $p < 0.01$).[37] In these studies a clear relationship was seen between bacterial eradication and antimicrobial potency (fig. 3). Gemifloxacin was significantly more effective against all strains of *S. pneumoniae* compared with ciprofloxacin and levofloxacin ($p < 0.01$).[37,38]

• In the same model, oral gemifloxacin 240 mg/kg/day initiated 24 hours postinoculation significantly reduced bacterial counts to below the level of detection (≤1.7 $\log_{10}$ cfu/lungs; $p < 0.01$) compared with controls (5.0 $\log_{10}$ cfu/lungs) in animals infected with a β-lactamase-negative ampicillin-resistant strain of *H. influenzae*.[38] Similar results were seen for a β-lactamase-positive strain of *H. influenzae*. Results achieved with levofloxacin and ciprofloxacin were comparable to those of gemifloxacin against both strains.[38] Against a ciprofloxacin-resistant strain of *H. influenzae*, gemifloxacin significantly reduced bacterial numbers compared with controls (2.5 *vs* 5.1 $\log_{10}$ cfu/lungs, respectively). Results for gemifloxacin were comparable with those for levofloxacin (3.1 $\log_{10}$ cfu/lungs) but were significantly superior to those for ciprofloxacin (4.3 $\log_{10}$ cfu/lungs; $p < 0.01$).[37]

• In a rabbit model of meningitis due to penicillin-sensitive *S. pneumoniae*, intravenous gemifloxacin 5 mg/kg/h reduced CSF bacterial titres at a rate of –0.25 $\log_{10}$ cfu/ml/h. This was similar to the rate of bacterial killing obtained with ceftriaxone 10 mg/kg/h (–0.38 $\log_{10}$ cfu/ml/h).[39]

• In infant rats with experimental *S. pneumoniae* meningitis, intraperitoneal gemifloxacin 50 and 100 mg/kg produced survival rates of 80 and 83%, respectively ($p \leq 0.01$ *vs* vehicle-treated animals). These survival rates were similar to those observed with ciprofloxacin 100 mg/kg (100%) and levofloxacin 100 mg/kg (88%).[40]

• In an experimental model of skin and soft tissue infection in rats, oral gemifloxacin 240 mg/kg/day (started 1 hour postinoculation) significantly reduced the number of *S. pyogenes*, *S. epidermidis* and *S. aureus* from 6.5 to 3.2, from 5.8 to 3.5 and from 6.8 to 3.5 $\log_{10}$ cfu/wound, respectively, compared with controls ($p < 0.01$). Gemifloxacin was significantly more effective than ciprofloxacin against all strains tested in this model ($p < 0.01$), and was comparable to levofloxacin against staphylococci and significantly more effective against *S. pyogenes* ($p < 0.01$).[41]

Effects on Human Intestinal Microflora

• Numbers of enterobacteria, enterococci and streptococci were decreased versus placebo after

administration of oral gemifloxacin 320 mg/day for 7 days in 15 healthy volunteers.[42] A decrease in the number of lactobacilli and anaerobic cocci was also detected. No selection or overgrowth of gemifloxacin-resistant bacteria or yeasts was observed. Levels of all anaerobic and aerobic organisms normalised 49 days after withdrawal of gemifloxacin.[42]

2. Pharmacokinetic Properties

Absorption and Distribution

- The peak plasma gemifloxacin concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased linearly with dose after single oral gemifloxacin doses of 20 to 800mg in healthy volunteers (n = 19). After a dose of 320mg, a C_{max} of 1.48 mg/L was achieved in 1 hour (t_{max}) and AUC was 9.30 mg/L · h.[43]

- Repeated doses of oral gemifloxacin 320mg for 7 days in healthy volunteers (n = 6) resulted in a C_{max} of 1.82 mg/L on day 7 versus 2.01 mg/L on day 1. Virtually no accumulation of gemifloxacin was detected after repeated dosages of up to 640 mg/day.[44]

- In animal studies, tissue concentrations 30 minutes after administration of gemifloxacin 20 mg/kg were 9.5 to 26.1 times greater in the liver, stomach, small intestine and kidney compared with those in plasma. At the same time-point, concentrations in the spleen, submaxillary gland, heart, thymus, lymph node, large intestine, lung and caecum muscle were 1.3 to 4.4 times greater than those in plasma.[45]

- *In vitro* studies showed that serum protein binding of gemifloxacin ranged from 56.9 to 59.6%.[45]

Metabolism and Elimination

- Renal clearance of gemifloxacin was independent of dose, and was 151 ml/min (9.06 L/h) after a single oral dose of 320mg.[43] Over a dose range of 20 to 800mg, approximately 25 to 40% of the administered dose was excreted unchanged in the urine (28 to 30% after a 320mg dose).[43,46]

- The mean plasma elimination half-life ($t_{½}$) of gemifloxacin was 7.4 hours after single oral doses ranging from 20 to 800mg; the $t_{½}$ for the 320mg dose was 6.65 hours.[43]

Drug Interactions

- In 14 healthy volunteers, oral aluminium hydroxide/magnesium 880/780mg administered 10 minutes after oral gemifloxacin 320mg markedly reduced the AUC of gemifloxacin by approximately 85% versus gemifloxacin alone. Administration 3 hours before gemifloxacin reduced the AUC by 15%, whereas administration 2 hours afterwards did not have an appreciable effect. Concomitant aluminium hydroxide/magnesium had no effect on the t_{max} or $t_{½}$ of gemifloxacin.[47]

- In a randomised, double-blind, crossover trial, small increases in the $AUC_{0-\infty}$ and C_{max} of gemifloxacin 320mg (10 and 11%, respectively) were observed after concomitant administration of omeprazole 40 mg/day versus gemifloxacin alone in 12 healthy volunteers. These changes were similar or less marked than those observed with other quinolones and were not considered to be clinically significant; however, this could not be confirmed statistically because of large intrasubject variability.[48]

- No clinically significant interactions were observed between gemifloxacin 320mg and warfarin (titrated to achieve a stable international normalised ratio for prothrombin time of 1.3 to 1.8)[49] or theophylline 600 to 700 mg/day[50] in adult volunteers, or between gemifloxacin 320mg and digoxin 0.25mg in healthy elderly volunteers.[51]

3. Therapeutic Trials

Several phase II trials have been completed for gemifloxacin, but only preliminary results are available at present. Phase IIIa trials assessing the efficacy of gemifloxacin in acute exacerbations of chronic bronchitis, urinary tract infections, community-acquired pneumonia and sinusitis have been recently completed, but results have not yet been published.

- A successful bacteriological response was observed in 94.7% of patients with acute exacerbations of chronic bronchitis (n = 61) treated with oral gemifloxacin 320 mg/day. A successful clinical response was achieved in 92.3% of patients.[52]

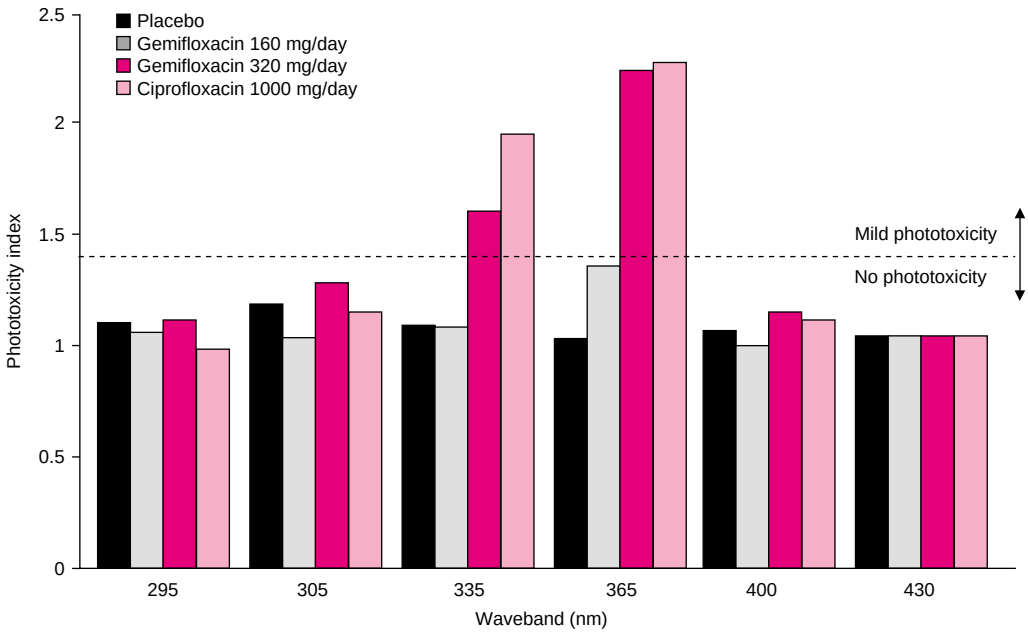


Fig. 4. Phototoxicity index (PI) of gemifloxacin, ciprofloxacin and placebo in healthy Caucasian volunteers (n = 38) in a randomised, double-blind trial. Volunteers received oral gemifloxacin 160mg or 320mg once daily, ciprofloxacin 500mg twice daily or placebo for 7 days. Mild phototoxicity was defined as a PI of between 1.4 and 3.[53]

• Clinical cure was reported in 98.7% of patients with uncomplicated urinary tract infections (n = 101) treated with oral gemifloxacin 320 mg/day, and 95% of patients achieved a bacteriological cure.[52]

4. Tolerability

• Results from phase II trials comparing gemifloxacin (n = 471) with ofloxacin (n = 206) show that gemifloxacin is well tolerated. Common adverse events with gemifloxacin included nausea (5.3%) and abdominal pain (3.6%); corresponding frequencies of nausea and abdominal pain after ofloxacin were 5.3 and 3.4%, respectively. There have been no reports of serious adverse events with gemifloxacin to date.[52]

• Multiple doses of gemifloxacin 320 mg/day were generally well tolerated by healthy volunteers with only headache being observed in 1 volunteer.[44] In volunteers taking part in drug interaction studies (section 2), headache, nausea and mild rash were reported.[47-51]

• No changes in ALT and AST levels were observed after gemifloxacin 320 mg/day.[44] At the 640mg dose, mild clinically asymptomatic, reversible increases in ALT and AST were seen in 3 out of 8 volunteers.[44] Urine crystal formation, considered to be associated with gemifloxacin, was observed in 1 volunteer with the 640 mg/day dose.[44]

• Gemifloxacin has a low potential for producing mild phototoxicity, and is similar to ciprofloxacin in this respect. In 38 healthy Caucasian volunteers, gemifloxacin 320 mg/day or ciprofloxacin 1000 mg/day administered for 7 days were associated with mean phototoxicity indices (PI) of 1.00 to 2.19 and 0.97 to 2.23, respectively (mild phototoxicity defined as PI = 1.4 to 3) [fig. 4]. Gemifloxacin 160 mg/day was associated with lower PI values than the 320 mg/day dose, suggesting that phototoxicity is dose-dependent. Susceptibility to photosensitivity cleared 48 hours after withdrawal of gemifloxacin.[53]

5. Gemifloxacin: Current Status

Gemifloxacin is a fluoroquinolone agent with an enhanced affinity for topoisomerase IV. Gemifloxacin has a broad spectrum of activity and, in par-

ticular, excellent potency against Gram-positive organisms including *S. pneumoniae*. Phase III clinical trials for gemifloxacin in the treatment of respiratory and urinary tract infections, sinusitis and acute exacerbations of chronic bronchitis have been completed and the drug has been filed for approval in the USA and Canada.

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