GENESOFT PHARMACEUTICALS INC
Form 425
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Filed by Genome Therapeutics Corp.

Pursuant to Rule 425 under the Securities Act of 1933

and deemed filed pursuant to Rule 14a-12

of the Securities Exchange Act of 1934

Subject Company: GeneSoft Pharmaceuticals, Inc.

Commission File No. 0-10824

This filing relates to the proposed merger transaction pursuant to the terms of that certain Agreement and Plan of Merger and Reorganization, dated as of November 17, 2003 (the Merger Agreement), by and among Genome Therapeutics Corp. (Genome Therapeutics), Guardian Acquisition, Inc., a wholly owned subsidiary of Genome Therapeutics, GeneSoft Pharmaceuticals, Inc. (Genesoft) and the Stockholders Representative named therein.

This filing is made for the purpose of filing certain prescribing information regarding FACTIVE®. The materials are also available on Genome Therapeutics website, www.genomecorp.com.

Forward-Looking Statements

This document may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements represent our management s judgment regarding future events. Forward-looking statements typically are identified by use of terms such as may, will, should, plan, expect, intend, anticipate, estimate, and similar words, although some forward-looking statements are expressed differently. We do not plan to update these forward-looking statements. You should be aware that our actual results could differ materially from those contained in the forward-looking statements due to a number of risks affecting our business. These factors include the risk that the proposed merger may not be approved by stockholders of Genome Therapeutics or Genesoft, Genome Therapeutics or Genesoft s inability to satisfy the closing conditions of the merger, including the condition of raising additional capital to finance the combined company, the risk that the two companies businesses will not be integrated successfully and the significant costs related to the proposed merger . Upon completion of the merger, our business will be significantly dependent upon the combined company s ability to launch the commercial sale of FACTIVE®, and, due to the limitations on our resources and experience in commercializing products, there can be no assurance that we will be able to successfully launch FACTIVE®. We continue to be subject to the risks related to our lead product candidate, Ramoplanin, such as (i) our inability to obtain regulatory approval to commercialize Ramoplanin due to negative, inconclusive or insufficient clinical data and (ii) delays in the progress of our clinical trials for Ramoplanin, and increased cost, due to the pace of enrollment of patients in the trials or fluctuations in the infection rate of enrolled patients. We are also subject to risks related to our inability or the inability of our alliance partners to (i) successfully develop products based on our genomics information, (ii) obtain the necessary regulatory approval for such products, (iii) effectively commercialize any products developed before our competitors are able to commercialize competing products or (iv) obtain and enforce intellectual property rights. In addition, we are subject to the risk factors set forth in Exhibit 99.1

to the Company s Quarterly Report on Form 10-Q for the quarter ended September 27, 2003 and those set forth in other filings that we may make with the Securities and Exchange Commission from time to time.

Additional Information About the Transaction and Where You Can Find It

Genome Therapeutics will file a proxy statement/prospectus and other documents concerning the proposed merger transaction with the SEC. **Investors are urged to read the proxy statement/prospectus when it becomes available and the other relevant documents filed with the SEC because they will contain important information.**

You will be able to obtain the proxy statement/prospectus and other related documents free of charge at the website maintained by the SEC at www.sec.gov. In addition, you may obtain documents filed with the SEC by Genome Therapeutics free of charge by requesting them in writing from Genome Therapeutics Corp., 100 Beaver Street, Waltham, MA 02453 Attention: Investor Relations, telephone: (781) 398-2300.

Genome Therapeutics and Genesoft and their respective directors, executive officers and other members of their management and employees, may be deemed to be participants in the solicitation of proxies from their respective shareholders in connection with the merger. Information about the directors and executive officers of Genome Therapeutics and their ownership of Genome Therapeutics shares is set forth in the proxy statement for Genome Therapeutics 2003 annual meeting of shareholders, filed with the SEC on April 2, 2003. Investors may obtain additional information regarding the interests of such participants by reading the proxy statement/prospectus when it is filed with the SEC.

This document shall not constitute an offer to sell or the solicitation of an offer to buy any securities of Genome Therapeutics.

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Labeling

July 17, 2003 version

PRESCRIBING INFORMATION

FACTIVE® (gemifloxacin mesylate) Tablets

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4*Z*)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]- 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 µg/mL at 37°C, pH 7.0). Its empirical formula is $C_{18}H_{20}FN_5O_4 \bullet CH_4O_3S$ and its chemical structure is:

Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

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CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40 mg to 640 mg. There was minimal accumulation of gemifloxacin following multiple oral doses up to 640 mg a day for 7 days (mean accumulation <20%). Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (Cmax) and systemic drug exposure (AUC(0-24)) were 1.61 ± 0.51 µg/mL (range 0.70-2.62 µg/mL) and 9.93 ± 3.07 µg•hr/mL (range 4.71-20.1 µg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC(0-24), 8.36 µg•hr/mL; range 3.2 47.7 µg•hr/mL.

The pharmacokinetics of gemifloxacin were not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore FACTIVE tablets may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60 to 70% and is concentration independent. After repeated doses, the in vivo plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66 12.12 L/kg).

Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in Table 1:

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Table 1. Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean±SD)
Plasma	1.40 (0.442) µg/mL	
Bronchoalveolar Macrophages	107 (77) µg /g	90.5(106.3)
Epithelial Lining Fluid	2.69 (1.96) µg /mL	1.99(1.32)
Bronchial Mucosa	9.52 (5.15) µg /g	7.21(4.03)

Metabolism

Gemifloxacin is metabolized to a limited extent by the liver. The unchanged compound is the predominant drug-related component detected in plasma (approximately 65%) up to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral dose); the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes is not significantly inhibited by gemifloxacin.

Excretion

Gemifloxacin and its metabolites are excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61± 9.5% of the dose was excreted in the feces and 36± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 L/hr (range 4.6-17.6 L/hr), which indicates active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady state following 320 mg to healthy subjects was approximately 7 ± 2 hours (range 4-12 hours).

Special Populations

Pediatric: The pharmacokinetics of gemifloxacin in pediatric subjects have not been studied.

Geriatric: In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age.

Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males.

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Males and females had mean AUC values of 7.98 µg·h/mL (range, 3.21 42.71 µg·h/mL) and 8.80 µg·h/mL (range, 3.33 47.73 µg·h/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

Hepatic Insufficiency: The pharmacokinetics following a single 320 mg dose of gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) liver disease. There was a mean increase in AUC (0-inf) of 34% and a mean increase in Cmax of 25% in these patients with hepatic impairment compared to healthy volunteers.

The pharmacokinetics of a single 320 mg dose of gemifloxacin were also studied in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean increase in AUC (0-inf) of 45% and a mean increase in Cmax of 41% in these subjects with hepatic impairment compared to healthy volunteers.

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. (See **DOSAGE AND ADMINISTRATION**.)

Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin Cmax was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. (See **DOSAGE AND ADMINISTRATION.)**

Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential: In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg b.i.d., or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg b.i.d. and the photosensitivity potential for both drugs were statistically greater than that of placebo. Photosensitivity reactions were

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reported rarely in clinical trials with gemifloxacin (0.039%). (See **ADVERSE REACTIONS**.)

Drug-Drug Interactions

Antacids/Di- and Trivalent Cations: The systemic availability of gemifloxacin is significantly reduced when an aluminum-and magnesium-containing antacid is concomitantly administered (AUC decreased 85%; Cmax decreased 87%). Administration of an aluminum- and magnesium- containing antacid or ferrous sulfate (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking FACTIVE tablets.

Calcium carbonate (1000 mg) given either 2 hr before or 2 hr after gemifloxacin administration showed no notable reduction in gemifloxacin systemic availability. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, not clinically significant, decrease in gemifloxacin exposure [AUC (0-inf) decreased 21% and Cmax decreased].

Sucralfate: When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69% decrease in Cmax). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected; therefore FACTIVE should be taken at least 2 hours before sucralfate. (See **PRECAUTIONS.**)

In Vitro Metabolism: Results of in vitro inhibition studies indicate that hepatic cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin metabolism. Therefore gemifloxacin should not cause significant in vivo pharmacokinetic interactions with other drugs that are metabolized by CYP450 enzymes.

Theophylline: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of theophylline (300 to 400 mg b.i.d. to healthy male subjects).

Digoxin: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

Oral Contraceptives: The effect of an oral estrogen/progesterone contraceptive product (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for 6 days) in healthy female subjects indicates that concomitant administration caused an average reduction in gemifloxacin AUC and Cmax of 19% and 12%. These changes are not

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considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 µg/150 µg once daily for 21 days to healthy female subjects).

Cimetidine: Co-administration of a single dose of 320 mg gemifloxacin with cimetidine 400 mg four times daily for 7 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 6%, respectively. These increases are not considered clinically significant.

Omeprazole: Co-administration of a single dose of 320 mg gemifloxacin with omeprazole 40 mg once daily for 4 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 11%, respectively. These increases are not considered clinically significant.

Warfarin: Administration of repeated doses of gemifloxacin (320 mg once daily for 7 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-induced anticoagulant activity (i.e., International Normalized Ratios for Prothrombin Time). (See **PRECAUTIONS: Drug Interactions**.)

Probenecid: Administration of a single dose of 320 mg gemifloxacin to healthy subjects who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in gemifloxacin AUC(0-inf) and a prolongation of mean half-life by 1.6 hours. Mean gemifloxacin Cmax increased 8%.

Microbiology

Gemifloxacin has in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for some of these double mutants.

The mechanism of action of quinolones, including gemifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin and other quinolones. There is no known cross-resistance between gemifloxacin and the above mentioned classes of antimicrobials.

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The main mechanism of fluoroquinolone resistance is due to mutations in DNA gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep mutations and efflux in a manner similar to other fluoroquinolones. The frequency of spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin.

Gemifloxacin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP])*.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae (many strains are only moderately susceptible)

Moraxella catarrhalis

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

The following data are available, **but their clinical significance is unknown.**

Gemifloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of 0.25 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Acinetobacter lwoffii

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Klebsiella oxytoca

Legionella pneumophila

Proteus vulgaris

Susceptibility Tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

MIC (µg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5	Intermediate (I)
≥1.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than Susceptible . Strains yielding MIC results suggestive of a nonsusceptible category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[b]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)

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0.25	Intermediate (I)
≥0.5	Resistant(R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Muller-Hinton broth with 2-5% lysed horse blood.

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of Intermediate indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gemifloxacin powder should provide the following MIC values:

Microorganism		**MIC Range (µg/mL)**
Enterococcus faecalis	ATCC 29212	0.016-0.12
Escherichia coli	ATCC 25922	0.004-0.016
Haemophilus influenzae	ATCC 49247[c]	0.002-0.008
Streptococcus pneumoniae	ATCC 49619[d]	0.008-0.03

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM)[1].

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum

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concentrations. This procedure uses paper disks impregnated with 5µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5µg gemifloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae:*

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
16-19	Intermediate (I)
≤15	Resistant (R)

For testing *Haemophilus influenzae and Haemophilus parainfluenzae*[e]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)

[e] This interpretive standard is applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than Susceptible . Strains yielding zone diameter results suggestive of a nonsusceptible category should be submitted to a reference laboratory for further testing.

For testing Streptococcus pneumoniae[f]:

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

f These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gemifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory

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procedures. For the diffusion technique, the 5µg gemifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-36
Haemophilus influenzae	ATCC 49247[g]	30-37
Streptococcus pneumoniae	ATCC 49619[h]	28-34

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2] .

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

FACTIVE is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES**.)

Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis*.

Community-acquired pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]) *, *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Klebsiella pneumoniae***.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

** In clinical trials, there were 13 subjects with *Klebsiella pneumoniae,* primarily from non-comparative studies. Ten subjects had mild disease, 2 had moderate disease, and 1 had severe disease. There were two clinical failures in subjects with mild disease (one subject with bacteriologic recurrence).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and

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susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Gemifloxacin is contraindicated in patients with a history of hypersensitivity to gemifloxacin, fluoroquinolone antibiotic agents, or any of the product components.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF FACTIVE IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy and Nursing Mothers subsections.)

QT Effects: **GEMIFLOXACIN MAY PROLONG THE QT INTERVAL IN SOME PATIENTS. GEMIFLOXACIN SHOULD BE AVOIDED IN PATIENTS WITH A HISTORY OF PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED ELECTROLYTE DISORDERS (HYPOKALEMIA OR HYPOMAGNESEMIA), AND PATIENTS RECEIVING CLASS IA (E.G., QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G., AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS.**

Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gemifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gemifloxacin treatment in over 6775 patients, including 653 patients concurrently receiving drugs known to prolong the QTc interval and 5 patients with hypokalemia.

The likelihood of QTc prolongation may increase with increasing dose of the drug; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours following oraladministration of gemifloxacin.

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy.

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These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

Gemifloxacin should be discontinued immediately at the appearance of any sign of an immediate type I hypersensitivity skin rash or any other manifestation of a hypersensitivity reaction**;** the need for continued fluoroquinolone therapy should be evaluated. As with other drugs, serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and occasionally fatal events, some due to hypersensitivity and/or some of uncertain etiology, have been reported in patients receiving fluoroquinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations usually include new onset fever and one or more of the following: rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Tendon and Cartilage Effects: Fluoroquinolones as a class have been shown to cause arthropathy and osteochondrosis in immature rats and dogs. The relevance of these findings to humans is unknown. Tendonitis and rupture of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving fluoroquinolones. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur either during or after treatment. Elderly patients, athletes, and patients taking corticosteroids are more prone to tendonitis.

CNS Effects: In clinical studies with gemifloxacin, Central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, gemifloxacin should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in gemifloxacin clinical trials, convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving other

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fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving gemifloxacin, the drug should be discontinued and appropriate measures instituted.

Antibiotic Associated Colitis: Pseudomembranous colitis has been reported with nearly all antibacterial agents, including gemifloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. (See **ADVERSE REACTIONS.**)

PRECAUTIONS

General: Prescribing FACTIVE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increase the risk of the development of drug-resistant bacteria.

Rash: In clinical studies, the overall rate of drug-related rash was 2.8%. The most common form of rash associated with gemifloxacin was described as maculopapular and mild to moderate in severity; 0.3% was described as urticarial in appearance. Rash usually appeared 8 to 10 days after start of therapy; 60% of the rashes resolved within 7 days, and 80% resolved within 14 days. Approximately 10% of those patients developing rash had a rash described as of severe intensity. Histology was evaluated in a clinical pharmacology study and was consistent with an uncomplicated exanthematous skin reaction and showed no evidence of phototoxicity, vasculitis, or necrosis. There were no documented cases in the clinical trials of more serious skin reactions known to be associated with significant morbidity or mortality.

Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). Prolonging duration of therapy beyond

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7 days causes the incidence of rash to increase significantly in all subgroups except men over the age of 40 (see Table 2). Gemifloxacin therapy should be discontinued in patients developing a rash while on treatment (see **ADVERSE REACTIONS** and **CLINICAL STUDIES**).

Table 2. Rash Incidence in Gemifloxacin Treated Patients from the Clinical Studies Population* by Gender, Age, and Duration of Therapy

Gender & Age (yr) Category	Duration of Gemifloxacin Therapy			
	5 days	7 days	10 days**	14 days**
Female < 40	5/242 (2.1%)	39/324 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥ 40	19/1210 (1.6%)	30/695 (4.3%)	19/308 (6.2%)	10/126 (7.9%)
Male < 40	4/218 (1.8%)	20/318 (6.3%)	7/74 (9.5%)	3/39 (7.7%)
Male ≥ 40	9/1321 (0.7%)	23/776 (3.0%)	9/345 (2.6%)	3/116 (2.6%)
Totals	37/2991 (1.2%)	112/2113 (5.3%)	55/858 (6.4%)	23/312 (7.4%)

* includes patients from studies of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and other indications.

** exceeds the recommended duration of therapy (see **DOSAGE AND ADMINISTRATION.**)

Photosensitivity reactions have been reported very rarely in clinical trials with FACTIVE. (See **CLINICAL PHARMACOLOGY.**) However, as with all drugs of this class, it is recommended that patients avoid unnecessary exposure to strong sunlight or artificial UV rays (e.g., sunlamps, solariums), and should be advised of the appropriate use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued if a photosensitivity reaction is suspected.

Hepatic Effects: Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving gemifloxacin 320 mg daily relative to comparator antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil, amoxicillin/clavulanate potassium, and ofloxacin). In patients who received gemifloxacin at doses of 480 mg per day or greater there was an increased incidence of elevations in liver enzymes. (See **ADVERSE REACTIONS**.)

There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy. The recommended dose of gemifloxacin 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded. (See **DOSAGE AND ADMINISTRATION**.)

Alteration of the dosage regimen is necessary for patients with impairment of renal function (creatinine clearance ≤ 40 mL/min). (See **DOSAGE AND ADMINISTRATION.**)

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Adequate hydration of patients receiving gemifloxacin should be maintained to prevent the formation of a highly concentrated urine.

Information for Patients

Patients should be advised:

- that antibacterial drugs including FACTIVE should only be used to treat bacterial infections. They do not treat viral infections (e.g. common cold). When FACTIVE is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance;

- that FACTIVE has been associated with rash. Patients should discontinue drug and call their healthcare provider if they develop a rash;

- that FACTIVE may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose; patients should immediately discontinue the drug at the sign of a rash or other allergic reaction and seek medical care;

- that FACTIVE may produce changes in the electrocardiogram (QTc interval prolongation);

- that FACTIVE should be avoided in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;

- that FACTIVE should be used with caution in patients receiving drugs that may affect the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants;

- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia;

- to inform their physician of any other medications when taken concurrently with FACTIVE, including over-the-counter medications and dietary supplements;

- to contact their physician if they experience palpitations or fainting spells while taking FACTIVE;

- that FACTIVE may be taken with or without meals;

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- to drink fluids liberally;

- not to take antacids containing magnesium and/or aluminum or products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution within 3 hours before or 2 hours after taking FACTIVE tablets;

- that FACTIVE should be taken at least 2 hours before sucralfate;

- that phototoxicity has been reported with certain quinolones. The potential for FACTIVE to cause phototoxicity was low (3/7659) at the recommended dose in clinical studies. In keeping with good clinical practice, avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds). If a sunburn-like reaction or skin eruption occurs, contact your physician; (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**);

- that FACTIVE may cause dizziness; if this occurs, patients should not operate an automobile or machinery or engage in activities requiring mental alertness or coordination;

- that they should discontinue FACTIVE therapy and inform their physician if they feel pain, tenderness or rupture of a tendon. Patients should rest and avoid exercise until the diagnosis of tendonitis or tendon rupture has been excluded;

- that convulsions have been reported in patients receiving quinolones; and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: Administration of repeat doses of FACTIVE had no effect on the repeat dose pharmacokinetics of theophylline, digoxin or an ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. (See **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**.)

Concomitant administration of FACTIVE and calcium carbonate, cimetidine, omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in the pharmacokinetics of gemifloxacin, which were considered to be without clinical significance. (See **CLINICAL PHARMACOLOGY.**)

Concomitant administration of FACTIVE with probenecid resulted in a 45% increase in systemic exposure to gemifloxacin. (See **CLINICAL PHARMACOLOGY**.)

FACTIVE had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy. However, because some quinolones have been reported to

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enhance the anticoagulant effects of warfarin or its derivatives in patients, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of an antacid containing aluminum and magnesium. Magnesium- and/or aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after FACTIVE. Sucralfate should not be taken within 2 hours of FACTIVE. (See **CLINICAL PHARMACOLOGY.**)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long term studies in animals to determine the carcinogenic potential of gemifloxacin have not been conducted.

Photocarcinogenesis: Gemifloxacin did not shorten the time to development of UVR-induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photocarcinogenic in this model. These mice received oral gemifloxacin and concurrent irradiation with simulated sunlight 5 days per week for 40 weeks followed by a 12-week treatment-free observation period. The daily dose of UV radiation used in this study was approximately $^{1}/_{3}$ of the minimal dose of UV radiation that would induce erythema in Caucasian humans. The median time to the development of skin tumors in the hairless mice was similar in the vehicle control group (36 weeks) and those given up to 100 mg/kg gemifloxacin daily (39 weeks). Following repeat doses of 100 mg/kg gemifloxacin per day, the mice had skin gemifloxacin concentrations of approximately 7.4 µg/g. Plasma levels following this dose were approximately 1.4 µg/mL in the mice around the time of irradiation. There are no data on gemifloxacin skin levels in humans, but the mouse plasma gemifloxacin levels are in the expected range of human plasma Cmax levels (0.7-2.6 µg/mL, with an overall mean of about 1.6 µg/mL) following multiple 320 mg oral doses.

Mutagenesis: Gemifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in an Ames *Salmonella* reversion assay. It did not induce micronuclei in the bone marrow of mice following intraperitoneal doses of up to 40 mg/kg and it did not induce unscheduled DNA synthesis in hepatocytes from rats which received oral doses of up to 1600 mg/kg. Gemifloxacin was clastogenic in vitro in the mouse lymphoma and human lymphocyte chromosome aberration assays. It was clastogenic *in vivo* in the rat micronucleus assay at oral and intravenous dose levels (≥800 mg/kg and ≥40 mg/kg, respectively) that produced bone marrow toxicity. Fluoroquinolone clastogenicity is

apparently due to inhibition of mammalian topoisomerase activity which has threshold implications.

Impairment of Fertility: Gemifloxacin did not affect the fertility of male or female rats at AUC levels following oral administration (216 and 600 mg/kg/day) that were approximately 3- to 4-fold higher than the AUC levels at the clinically recommended dose.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing at 450 mg/kg/day), rats (oral dosing at 600 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day) at AUC levels which were 2-, 4- and 3-fold those in women given oral doses of 320 mg. In rats, this growth retardation appeared to be reversible in a pre- and postnatal development study (mice and rabbits were not studied for the reversibility of this effect). Treatment of pregnant rats at 8-fold clinical exposure (based upon AUC comparisons) caused fetal brain and ocular malformations in the presence of maternal toxicity. The overall no-effect exposure level in pregnant animals was approximately 0.8 to 3-fold clinical exposure.

The safety of gemifloxacin in pregnant women has not been established. Gemifloxacin should not be used in pregnant women unless the potential benefit to the mother outweighs the risk to the fetus. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers: Gemifloxacin is excreted in the breast milk of rats. There is no information on excretion of gemifloxacin into human milk. Therefore, gemifloxacin should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

Pediatric Use: Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including gemifloxacin, cause arthropathy and osteochondrosis in immature animals. (See **WARNINGS.**)

Geriatric Use: Of the total number of subjects in clinical studies of gemifloxacin, 30% (2064) were 65 and over, while 12% (779) were 75 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse event rates for this group was similar to or lower than that for younger subjects with the exception that the incidence of rash was lower in geriatric patients compared to patients less than 40 years of age.

ADVERSE REACTIONS

In clinical studies, 6775 patients received daily oral doses of 320 mg gemifloxacin. In addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of gemifloxacin in clinical pharmacology studies. The majority of

adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity.

Gemifloxacin was discontinued because of an adverse event (possibly or probably related) in 2.2% of patients, primarily due to rash (0.9%), nausea (0.3%), diarrhea (0.3%), urticaria (0.3%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an adverse event at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.3%), vomiting (0.3%) and rash (0.3%).

Drug-related adverse events, classified as possibly or probably related with a frequency of ≥1% for patients receiving 320 mg of gemifloxacin versus comparator drug (beta-lactam antibiotics, macrolides or other fluoroquinolones) are as follows: diarrhea 3.6% vs. 4.6%; rash 2.8% vs. 0.6%; nausea 2.7% vs. 3.2%; headache 1.2% vs. 1.5%; abdominal pain 0.9% vs. 1.1%; vomiting 0.9% vs. 1.1%; dizziness 0.8% vs. 1.5%; and taste perversion 0.3% vs. 1.9%.

Gemifloxacin appears to have a low potential for photosensitivity. In clinical trials, treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.

Additional drug-related adverse events (possibly or probably related) in ≥0.1% to 1% of patients who received 320 mg of gemifloxacin were: abdominal pain, anorexia, arthralgia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, hyperglycemia, insomnia, leukopenia, moniliasis, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

Other adverse events reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in ≥0.1% of patients were: abnormal urine, anemia, asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, flushing, gastroenteritis, granulocytopenia, hot flashes, increased GGT, leg cramps, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, pneumonia, thrombocyotopenia, tremor, vertigo, and vision abnormality.

In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), the incidences of rash were as follows (Table 3):

Table 3. Incidence of Rash by Clinical Indication in Patients Treated with Gemifloxacin

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	ABECB (5 days) N = 2284		CAP (7 days) N = 643	
	n/N	%	n/N	%
Totals	27/2284	1.2	26/643	4.0
Females, < 40 years	NA*		8/88	9.1
Females, ≥ 40 years	16/1040	1.5	5/214	2.3
Males, < 40 years	NA*		5/101	5.0
Males, ≥ 40 years	11/1203	0.9	8/240	3.3

* insufficient number of patients in this category for a meaningful analysis

(see **PRECAUTIONS**)

Laboratory Changes: The percentages of patients who received multiple doses of gemifloxacin and had a laboratory abnormality are listed below. It is not known whether these abnormalities were related to gemifloxacin or an underlying condition.

Clinical Chemistry: increased ALT (1.5%), increased AST (1.1%), increased creatine phosphokinase (0.6%), increased potassium (0.5%), decreased sodium (0.3%), increased gammaglutamyl transferase (0.5%), increased alkaline phosphatase (0.3%), increased total bilirubin (0.3%), increased blood urea nitrogen (0.3%), decreased calcium (0.2%), decreased albumin (0.3%), increased serum creatinine (0.2%), decreased total protein (0.1%) and increased calcium (<0.1%).

CPK elevations were noted infrequently: 0.8% in gemifloxacin patients vs. 0.4% in the comparator patients.

Hematology: increased platelets (0.9%), decreased neutrophils (0.5%), increased neutrophils (0.5%), decreased hematocrit (0.3%), decreased hemoglobin (0.2%), decreased platelets (0.2%), decreased red blood cells (0.1%), increased hematocrit (0.1%), increased hemoglobin (0.1%), and increased red blood cells (0.1%).

In clinical studies, approximately 7% of the gemifloxacin treated patients had elevated ALT values immediately prior to 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 evidence of hepatocellular jaundice. For the pooled comparators, approximately 6% of patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 7% showed a further elevation of

their ALT at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

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In a clinical trial where 638 patients received either a single 640 mg dose of gemifloxacin or 250 mg bid of ciprofloxacin for 3 days, there was an increased incidence of ALT elevations in the gemifloxacin arm (3.9%) vs. the comparator arm (1.0%). In this study, two patients experienced ALT elevations of 8 to 10 times the upper limit of normal. These elevations were asymptomatic and reversible.

OVERDOSAGE

Any signs or symptoms of overdosage should be treated symptomatically. No specific antidote is known. In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage; the patient should be carefully observed and treated symptomatically with appropriate hydration maintained. Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400 mg/kg) of gemifloxacin to rodents included ataxia, lethargy, piloerection, tremor, and clonic convulsions.

DOSAGE AND ADMINISTRATION

FACTIVE can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of FACTIVE is 320 mg daily, according to the following table (Table 4).

Table 4. Recommended Dosage Regimen of FACTIVE

INDICATION	DOSE	DURATION
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily	5 days
Community-acquired pneumonia (of mild to moderate severity)	One 320 mg tablet daily	7 days

The recommended dose and duration of FACTIVE should not be exceeded (see Table 2).

Renally Impaired Patients: Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. Table 5 provides dosage guidelines for use in patients with renal impairment:

Table 5. Recommended Doses for Patients with Renal Impairment

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Creatinine Clearance (mL/min)	Dose
>40	See Usual Dosage
≤40	160 mg q24h

Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) should receive 160 mg q24h.

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine Clearance (mL/min) = Weight (kg) x (140 age)

72 x serum creatinine (mg/dL)

Women: 0.85 x the value calculated for men

Use in Hepatically Impaired Patients: No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Use in Elderly: No dosage adjustment is recommended.

HOW SUPPLIED

FACTIVE (gemifloxacin mesylate) is available as white to off-white, oval, film-coated tablets with breaklines and GE 320 debossed on both faces. Each tablet contains gemifloxacin mesylate equivalent to 320 mg of gemifloxacin.

320 mg Unit of Use (CR*) 5 s	NDC 67707-320-05
320 mg Unit of Use (CR*) 7 s	NDC 67707-320-07
320 mg Hospital Pack (NCR**) 30 s	NDC 67707-320-30

*Child Resistant **Not Child Resistant

STORAGE

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. Degeneration of articular cartilage occurred in juvenile dogs given at least 192 mg/kg/day gemifloxacin in a

28-day study (producing about 6 times the systemic exposure at the clinical dose), but not in mature dogs. There was no damage to the articular surfaces of joints in immature rats given repeated doses of up to 800 mg/kg/day.

Some quinolones have been reported to have proconvulsant properties that are potentiated by the concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs). Gemifloxacin alone had effects in tests of behaviour or CNS interaction typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the active metabolite of the NSAID, fenbufen, followed by 80 mg/kg gemifloxacin.

Dogs given 192 mg/kg/day (about 6 times the systemic exposure at the clinical dose) for 28 days, or 24 mg/kg/day (approximately equivalent to the systemic exposure at the clinical dose) for 13 weeks showed reversible increases in plasma ALT activities and local periportal liver changes associated with blockage of small bile ducts by crystals containing gemifloxacin.

Quinolones have been associated with prolongation of the electrocardiographic QT interval in dogs. Gemifloxacin produced no effect on the QT interval in dogs dosed orally to provide about 4 times human therapeutic plasma concentrations at Cmax, and transient prolongation after intravenous administration at more than 4 times human plasma levels at Cmax. Gemifloxacin exhibited weak activity in the cardiac I_{Kr} (hERG) channel inhibition assay, having an IC_{50} of approximately 270 μM.

Gemifloxacin, like many other quinolones, tends to crystallize at the alkaline pH of rodent urine, resulting in a nephropathy in rats that is reversible on drug withdrawal (oral no-effect dose 24 mg/kg/day).

Gemifloxacin was weakly phototoxic to hairless mice given a single 200 mg/kg oral dose and exposed to UVA radiation, however, no evidence of phototoxicity was observed at 100 mg/kg/day dosed orally for 13 weeks in a standard hairless mouse model, using simulated sunlight.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

FACTIVE (320 mg once daily for 5 days) was evaluated for the treatment of acute bacterial exacerbation of chronic bronchitis in three pivotal double-blind, randomized, actively-controlled clinical trials (studies 068, 070, and 212). The primary efficacy parameter in these studies was the clinical response at follow-up (day 13 to 24). The results of the clinical response at follow-up for the principal ABECB studies demonstrate that FACTIVE 320 mg PO once daily for 5 days was at least as good as the comparators given for 7 days. The results are shown in Table 6 below.

Table 6. Clinical Response at Follow-Up (Test of Cure): Pivotal ABECB Studies

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Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
	Study 068	
FACTIVE 320 mg	86.0 (239/278)	1.2 (-4.7, 7.0)
x 5 days		
Clarithromycin 500 mg	84.8 (240/283)	
bid x 7 days		
	Study 070	
FACTIVE 320 mg	93.6 (247/264)	0.4 (-3.9, 4.6)
x 5 days		
Amoxicillin/clavulanate	93.2 (248/266)	
500 mg/125 mg tid		
x 7 days		
	Study 212	
FACTIVE 320 mg	88.2 (134/152)	3.1 (-4.7, 10.7)
x 5 days		
Levofloxacin 500 mg	85.1 (126/148)	
x 7 days		

Community Acquired Pneumonia (CAP)

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of community acquired pneumonia in adults consisted of three double-blind, randomized, actively-controlled clinical studies (studies 011, 012, and 049) and one open, actively-controlled study (study 185). In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the studies, pivotal study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for FACTIVE. Pivotal study 011 compared a 7-day course of FACTIVE with a 10-day treatment course of amoxicillin/clavulanate (1g/125 mg tid) and clinical success rates were similar between treatment arms. The results of comparative studies 049, 185, and 012 were supportive although treatment duration could have been 7 to 14 days. The results of the clinical studies with a fixed 7-day duration are shown in Table 7:

Table 7. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7 Day Duration of Treatment

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Labeling

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
	Study 011	
FACTIVE 320 mg x 7 days	88.7% (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 500 mg/125 mg tid x 10 days	87.6% (99/113)	
	Study 061	
FACTIVE 320 mg x 7 days	91.7%(154/168)	(86.1, 95.2)
	Study 287	
FACTIVE 320 mg x 7 days	89.8% (132/147)	(84.9, 94.7)

* For uncontrolled studies, the 95% CI around the success rate is shown

The combined bacterial eradication rates for patients treated with a fixed 7-day treatment regimen of FACTIVE are shown in Table 8:

Table 8. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies with a Fixed 7-day Duration of Treatment

Pathogen	n/N	%
S. pneumoniae	68/77	88.3
M. pneumoniae	21/22	95.5
H. influenzae	30/35	85.7
C. pneumoniae	13/14	92.9
*K. pneumoniae**	11/13	84.6
M. catarrhalis	10/10	100

* Subjects with *Klebsiella pneumoniae* included in this table were from non-comparative studies 061 and 287. 10 of these subjects had mild disease, 2 had moderate disease, and 1 had severe disease. Both failures were in subjects with mild disease (one of these had a bacteriologic recurrence).

FACTIVE was also effective for the treatment of CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP*). Of 22 patients with MDRSP treated for 7 days, 19 (86.5%) achieved clinical and bacteriological success at follow-up. The clinical and bacteriological success for the 22 patients with 22 MDRSP isolates are shown in Table 9.

*MDRSP: Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

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Table 9. Clinical and Bacteriological Success for 22 Patients Treated with FACTIVE in Studies with a 7-day Duration of Treatment for MDRSP

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N[a]	%	n/N[b]	%
Penicillin-resistant	11/11	100	11/11	100
2nd generation cephalosporin-resistant	14/14	100	14/14	100
Macrolide-resistant[c]	16/19	84.2	16/19	84.2
Trimethoprim/sulfamethoxazole-resistant	16/16	100	16/16	100
Tetracycline-resistant	13/16	81.3	13/16	81.3

a) n = the number of patients successfully treated; N = number of patients with MDRSP (from a total of 22 patients)

b) n = the number of bacteriological isolates successfully treated; N = number of isolates studied (from a total of 22 isolates)

c) Macrolide antibiotics tested include clarithromycin and erythromycin

Cutaneous Manifestations (Rash)

In clinical trials of 6,775 patients, the incidence of rash was higher in patients receiving gemifloxacin than in those receiving comparator drugs (see **PRECAUTIONS** and **ADVERSE REACTIONS**). Rash was more commonly observed in patients <40 years of age, especially females and post-menopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). (See Table 2.)

To further characterize gemifloxacin-associated rash, a clinical pharmacology study was conducted. The study enrolled 1,011 healthy female volunteers less than 40 years of age. Subjects were randomized to receive either FACTIVE 320 mg po daily or ciprofloxacin 500 mg po twice daily for 10 days. The objective of the study was to assess the characteristics of rash. The majority of rashes in subjects receiving FACTIVE were maculopapular and of mild to moderate severity; 7% of the rashes were reported as severe, and severity appeared to correlate with the extent of the rash. In 68% of the subjects reporting a severe rash and approximately 25% of all those reporting rash, >60% of the body surface area was involved; the characteristics of the rash were otherwise indistinguishable from those subjects reporting a mild rash. The histopathology was consistent with the clinical observation of uncomplicated exanthematous morbilliform eruption. There were no documented cases of hypersensitivity syndrome or findings suggestive of angioedema or other serious cutaneous reactions.

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The majority of rash events (81.9%) occurred on days 8 through 10 day of the planned 10 day course of gemifloxacin; 2.7% of rash events occurred within one day of the start of dosing. The median duration of rash was 6 days. The rash resolved without treatment in the majority of subjects. Approximately 19% received antihistamines and 5% received steroids, although the therapeutic benefit of these therapies is uncertain.

In the second part of this study after a 4 to 6 week wash out period, subjects developing a rash on gemifloxacin were treated with ciprofloxacin or placebo; 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash when treated with placebo. The characteristics of rash in subjects receiving ciprofloxacin following gemifloxacin were similar to those described in subjects who only received ciprofloxacin. The cross sensitization rate to other fluoroquinolones was not evaluated in this clinical study. There was no evidence of sub-clinical sensitization to gemifloxacin (i.e. subjects who had not developed a rash to gemifloxacin in the first part of the study were not at higher risk of developing a rash to gemifloxacin with a second exposure).

There was no relationship between the incidence of rash and systemic exposure (Cmax and AUC) to either gemifloxacin or its major metabolite, N-acetyl gemifloxacin.

REFERENCES: 1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003. **2.** National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests Eighth Edition. Approved Standard NCCLS Document A2-A8, Vol. 23, No. 1, NCCLS Wayne, PA, January 2003.

Patient Information

This leaflet summarizes the most important information about FACTIVE. Read the Patient Information that comes with FACTIVE each time you get a new prescription. There may be new information. This leaflet does not list all benefits and risks of treatment and does not take the place of talking with your healthcare provider about your condition or your treatment. FACTIVE can only be prescribed by a healthcare professional. If you would like more information, talk with your healthcare provider or pharmacist.

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What is FACTIVE?

FACTIVE is an antibiotic. It is used to treat adults 18 years or older with bronchitis or pneumonia (lung infections) caused by certain bacteria (germs).

Sometimes, other germs called viruses infect the lungs. The common cold is a virus. FACTIVE, like other antibiotics, does not treat viruses.

FACTIVE tablets are white to off white and imprinted with GE 320 on both sides.

Who should not take FACTIVE?

- **Do not take FACTIVE if you are allergic to any of the ingredients in FACTIVE or to any antibiotic called a quinolone .** If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, stop taking FACTIVE and call your healthcare professional. The ingredients in FACTIVE are listed at the end of this leaflet. Ask your healthcare provider or pharmacist if you need a list of quinolones.

FACTIVE may not be right for you. Tell your healthcare provider if you:

- are pregnant, planning to become pregnant, or are breast feeding The effects of FACTIVE on unborn children and nursing infants are unknown;
- or any family members have a rare heart condition known as congenital prolongation of the QTc interval;
- have low potassium or magnesium levels;
- have a slow heart beat called bradycardia;
- have had a recent heart attack;
- have a history of convulsions;
- have kidney problems.

FACTIVE has not been studied in children under the age of 18. Quinolones may cause joint problems (arthropathy) in children.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and dietary supplements. **Be sure to tell your healthcare provider if you take:**

- medicines for your heart rhythm called antiarrhythmics
- erythromycin
- medicines for your mental health called antipsychotics or tricyclic antidepressants

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- medicines called corticosteroids , taken by mouth or by injection
- medicines called diuretics such as furosemide and hydrochlorothiazide.

How should I take FACTIVE?

- Take 1 FACTIVE tablet a day for 5 or 7 days, exactly as prescribed.
- Take FACTIVE at the same time each day.
- FACTIVE can be taken with or without food.
- Swallow the FACTIVE tablet whole, and drink plenty of fluids with it. Do not chew the FACTIVE tablet.
- If you miss a dose of FACTIVE, take it as soon as you remember. **Do not take more than 1 dose of FACTIVE in a day.**
- To make sure all bacteria are killed, take all the medicine that was prescribed for you even if you begin to feel better.
- Call your healthcare provider if your condition does not improve while taking FACTIVE.

Do not take the following medicines within 3 hours before FACTIVE or 2 hours after FACTIVE. They may interfere with the absorption of FACTIVE and may prevent it from working properly:

- antacids that contain magnesium or aluminum
- ferrous sulfate (iron)
- multivitamin that contains zinc or other metals
- Videx® (didanosine)

FACTIVE should be taken at least 2 hours before sucralfate.

What are possible side effects of FACTIVE?

FACTIVE is generally well tolerated. The most common side effects with FACTIVE include diarrhea, rash, nausea, headache, vomiting, stomach pain, dizziness, and a change in the way things taste in your mouth. If you get a rash while taking FACTIVE, stop FACTIVE, and call your healthcare provider right away. Do not drive or operate heavy machinery until you know how FACTIVE affects you. FACTIVE can make you dizzy.

FACTIVE and other quinolone antibiotics may cause the following serious side effects:

- a rare heart problem known as prolongation of the QTc interval. This condition can cause an abnormal heartbeat and result in sudden death. You should call your healthcare provider right away if you have any symptoms of prolongation of the QTc interval including heart palpitations (a change in the way your heart beats) or fainting spells;

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- central nervous system problems including body shakes (tremors), restless feeling, lightheaded feelings, confusion, and hallucinations (seeing or hearing things that are not there);
- tendon problems including tendonitis or rupture (tears) of a tendon. If you experience pain, swelling, or rupture of a tendon, stop taking FACTIVE and call your healthcare professional;
- phototoxicity. This can make your skin sunburn easier. Do not use a sunlamp or tanning bed while taking FACTIVE. Use a sunscreen and wear protective clothing if you must be out in the sun;

These are not all the side effects you may experience with FACTIVE. If you get any side effects that concern you, call your healthcare provider.

General information about the safe and effective use of FACTIVE:

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use FACTIVE for a condition for which it was not prescribed. Do not give FACTIVE to other people, even if they have the same symptoms that you have. It may harm them. **Keep FACTIVE and all medicines out of the reach of children.**

What are the ingredients in FACTIVE?

Active ingredient: gemifloxacin

Inactive Ingredients: crospovidone, hydroxypropyl methycellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide.

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Rx only

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