Fluoroquinolones, including FACTIVE®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS). Fluoroquinolones, including FACTIVE, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid FACTIVE in patients with known history of myasthenia gravis (See WARNINGS).

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-[(4Z)-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 C18H20FN5O4•CH4O3S and its chemical structure is:

![Chemical structure of gemifloxacin](image_url)

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.

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% Cl 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal plasma gemifloxacin concentrations (Cmax) and systemic pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 µg•hr/mL (range, 3.21 – 42.71 µg•hr/mL) and 8.80 µg•hr/mL (range, 3.33 – 47.73 µg•hr/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.

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 BID, 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 range), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg BID and the photosensitivity potential for both drugs was statistically greater than that of placebo. Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin (0.53%). (See ADVERSE REACTIONS.)

It is difficult to ascribe relative photosensitivity/phototoxicity among various fluoroquinolones during actual patient use because other factors play a role in determining a subject's susceptibility to this adverse event such as: a patient's skin pigmentation, frequency and duration of sun and artificial ultraviolet light (UV) exposure, wearing of sun screen and protective clothing, the use of other concomitant drugs and the dosage and duration of fluoroquinolone

Reference ID: 3356620
therapy. (See ADVERSE REACTIONS and ADVERSE REACTIONS: Post-Marketing Adverse Reactions.)

Drug-Drug Interactions
Antacid/Dr- and Trivalent Cations: The systemic availability of gemifloxacin is significantly reduced when an aluminum- and magnesium-containing antacid is concomitantly administered (AUC decreased 89%; 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 Vixid® (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 hr 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 BID 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/progestogen 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 considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrel 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 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. However, the presence of double mutants was not evaluated in clinical trials; therefore, the clinical significance of these in vitro data are unknown.

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.

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 in both DNA gyrase and TOPO IV (double mutants) are resistant to most 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 (MIC ≥2 μg/mL), 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 baumannii
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 (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 Klebsiella pneumoniae:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.12</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

For testing Haemophilus influenzae and Haemophilus parainfluenzae:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.12</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

1 These interpretive standard is applicable only to broth microdilution susceptibility testing with Haemophilus influenzae and Haemophilus parainfluenzae using Haemophilus Test Medium (HTM).

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:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.12</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.12</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

1 These interpretive standards are applicable only to broth microdilution susceptibility testing using cation-adjusted Mueller-Hinton broth with 2.5%-laked 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. Standardized gemifloxacin powder should provide the following MIC values:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>MIC Range (µg/mL)</th>
<th>Reference ID: 3356620</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>ATCC 25922</td>
<td>0.004-0.16</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>ATCC 49247</td>
<td>0.002-0.009</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>ATCC 49619</td>
<td>0.008-0.03</td>
</tr>
</tbody>
</table>

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

This quality control range is applicable to only S. pneumoniae ATCC 49619 tested by a broth microdilution procedure using 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 procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.

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

For testing Klebsiella pneumoniae:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-19</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

For testing Haemophilus influenzae and Haemophilus parainfluenzae:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18</td>
<td>Susceptible (S)</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥23</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>20-22</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>≤19</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO₂.

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

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Zone Diameter (mm)</th>
<th>Reference ID: 3356620</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>ATCC 25922</td>
<td>29-36</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>ATCC 49247</td>
<td>30-37¹</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>ATCC 49619</td>
<td>28-34¹</td>
</tr>
</tbody>
</table>

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

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% CO₂.

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]²), Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae, or Klebsiella pneumoniae.

² 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 (MIC ≥2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

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

WARNINGS
Tendinopathy and Tendon Rupture: Fluoroquinolones, including FACTIVE, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. FACTIVE should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Exacerbation of Myasthenia Gravis: Fluoroquinolones, including FACTIVE, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid FACTIVE in patients with known history of myasthenia gravis. (See PRECAUTIONS/Information for Patients and Adverse Reactions/Post-Marketing Adverse Reactions.)

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: Fluoroquinolones may prolong the QT interval in some patients. FACTIVE 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. FACTIVE 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 FACTIVE treatment in over 8119 patients, including 707 patients concurrently receiving drugs known to prolong the QTc interval and 7 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 oral administration of gemifloxacin.

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

FACTIVE 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.)

Other serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including FACTIVE. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, 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.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS).

Peripheral Neuropathy: Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including FACTIVE. Symptoms may occur soon after initiation of FACTIVE and may be irreversible. FACTIVE should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy, including pain, burning, tingling, numbness, and/or weakness or other alterations in sensations involving small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness or other alterations in sensations.

CNS Effects: In clinical studies with FACTIVE, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, FACTIVE should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in FACTIVE clinical trials, convulsions, increased intracranial pressure (including pseudotumor cerebi), and toxic psychosis have been reported in patients receiving other fluoroquinolones 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 FACTIVE, the drug should be discontinued and appropriate measures instituted.

Clostridium difficile Associated Diarrhea: Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including FACTIVE, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibiotics and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

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

Rash: In clinical studies, rash occurred more often with FACTIVE than with comparator agents (2.7% vs. 0.6%). Increasing incidence of rash was associated with younger age (especially below 40), female gender, use of hormone replacement therapy and longer durations of therapy (see Table 2). Urticarial reactions, some of which were not classified as rash, were more common in FACTIVE patients than in comparator patients (0.6% vs. 0.2%). FACTIVE should be discontinued in patients developing a rash or urticaria while on treatment. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

Table 2. Rash Incidence in FACTIVE Treated Patients from the Clinical Studies

<table>
<thead>
<tr>
<th>Gender &amp; Age</th>
<th>5 days</th>
<th>7 days</th>
<th>10 days*</th>
<th>14 days**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female &lt; 40</td>
<td>10/399 (2.5%)</td>
<td>49/407 (12.6%)</td>
<td>20/131 (15.3%)</td>
<td>7/31 (22.6%)</td>
</tr>
<tr>
<td>Female ≥ 40</td>
<td>30/1438 (2.1%)</td>
<td>34/887 (3.8%)</td>
<td>19/308 (6.2%)</td>
<td>10/126 (7.9%)</td>
</tr>
<tr>
<td>Male &lt; 40</td>
<td>6/356 (1.7%)</td>
<td>26/452 (5.7%)</td>
<td>7/74 (9.5%)</td>
<td>3/36 (7.7%)</td>
</tr>
<tr>
<td>Male ≥ 40</td>
<td>10/245 (4.1%)</td>
<td>26/804 (2.6%)</td>
<td>9/345 (2.6%)</td>
<td>3/116 (2.6%)</td>
</tr>
</tbody>
</table>

*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)

The most common form of rash associated with FACTIVE was described as maculopapular and mild to moderate in severity. Eighty percent of rashes resolved within 14 days. Approximately 10% of the rashes (0.5% of all patients) were described as severe intensity and approximately 10% of those with rash were treated with systemic steroids. There were no documented cases in the clinical trials of more serious skin reactions known to be associated with significant morbidity or mortality.

Moderate to severe photosensitivity/photoxic reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, “V” area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with use of quinolones after sun or UV light exposure. Therefore excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs. (See ADVERSE REACTIONS and ADVERSE REACTIONS: Post-Marketing Adverse Reactions.)

Hepatic Effects: Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving FACTIVE 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 FACTIVE 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded. (See DOSAGE AND ADMINISTRATION.)

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

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

Information for Patients

Patients should be counseled:

- that peripheral neuropathies have been associated with FACTIVE use, that symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, patients should immediately discontinue FACTIVE and contact their physician.
- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue FACTIVE treatment. The risk of severe tendon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- that fluoroquinolones like FACTIVE may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems;
- that antibacterial drugs including FACTIVE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When FACTIVE is prescribed to treat a bacterial infection, patients should be told that 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 and will not be treatable by FACTIVE or other antibacterial drugs in the future;
- that FACTIVE has been associated with rash and hives. Rash occurs more commonly in those under 40, especially women and in women on hormone replacement therapy. The incidence of rash increases with duration more than 5 days and particularly longer than 7 days. Patients should discontinue FACTIVE 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 diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible;
- that FACTIVE may cause 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 affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia;
• to contact their physician if they experience palpitations or fainting spells while taking FACTIVE;
• 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 convulsions have been reported in patients receiving quinolones. Patients should notify their physician before taking FACTIVE if they have a history of convulsions, seizures, or epilepsy;
• that other central nervous system problems such as tremors, restlessness, lightheadedness, confusion and hallucinations may occur rarely;
• that photosensitivity phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UV/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician; (See CLINICAL PHARMACOLOGY: Photosensitivity Potential);
• that increases of the International Normalized Ratio (INR), or prothrombin time (PT) and/or clinical episodes of bleeding have been noted with concurrent administration of warfarin or its derivatives, and FACTIVE. Patients should notify their physicians if they are taking warfarin or its derivatives;
• to inform their physician of any other medications when taken concurrently with FACTIVE, including over-the-counter medications and dietary supplements;
• that FACTIVE may be taken with or without meals;
• to drink fluid 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 or 2 hours after sucralfate.

Drug Interactions: Admission of repeat doses, 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/progestrone 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, post-marketing reports of increases in the INR, or PT, and/or clinical episodes of bleeding in patients have been noted with the use of quinolones, including FACTIVE, and warfarin, or its derivatives. In addition, infectious disease and its accompanying inflammatory process, age and general status of the patient are risk factors for increased anticoagulation activity. Therefore, the INR, or PT or other suitable coagulation test should be closely monitored if a quinolone antimicrobial, including FACTIVE, 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 UVB-induced skin tumors in hairless albino (SH-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 tumors in the hairless mice was similar in the vehicle control group (36 weeks) and those given 40 mg/kg/day of gemifloxacin for 36 weeks. 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 FACTIVE in pregnant women has not been established. FACTIVE 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, FACTIVE 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: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as FACTIVE. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, head, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing FACTIVE to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue FACTIVE and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See Boxed Warning, WARNINGS, and ADVERSE REACTIONS/Post-Marketing Adverse Event Reports).

Of the total number of subjects in clinical studies of FACTIVE, 29% (2314) were 65 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse event rate 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.

Females patients may be more susceptible to drug-associated effects on the QT interval. Therefore, FACTIVE should be avoided in patients taking drugs that can result in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in patients with risk factors for torsades de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS
In clinical studies, 8119 patients received daily oral doses of 320 mg FACTIVE. In addition, 167 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.

FACTIVE was discontinued because of an adverse event (determined by the investigator to be possibly or probably related to drug) in 2.0% of patients, primarily due to rash (0.8%), nausea (0.3%), diarhoea (0.3%), urticaria (0.2%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an adverse event at an overall comparable rate of 2.1%, primarily rash, and may be more susceptible to drug-associated effects on the QT interval. Therefore, FACTIVE should be avoided in patients taking drugs that can result in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in patients with risk factors for torsades de pointes.

The most commonly reported adverse events with a frequency of ≥2% for patients receiving 320 mg FACTIVE versus comparator drug (beta-lactam antibiotics, macrolides or other fluoroquinolones) are as follows: diarrhea 5.0% vs. 6.2%; rash 3.5% vs. 1.1%; nausea 3.7% vs. 4.5%; headache 4.2% vs. 5.2%; abdominal pain 2.2% vs. 2.2%; vomiting 1.6% vs. 2.0%; and dizziness 1.7% vs. 2.6%.

Adverse Events with a Frequency of Less than 1%
Additional drug-related adverse events (possibly or probably related) in the 8119 patients included, with a frequency of >0.1% to ≤1% included: abdominal pain, anorexia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, genitai pruritus, hyperglycemia, increased alkaline phosphatase, increased ALT, increased AST, increased creatine phosphokinase, insomnia, leukopenia, pruritus, somnolence, taste perversion, thrombocytopenia, urticaria, vaginosis, 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, abdominal pain, anemia, arthralgia, arthrosis, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, facial edema, flushing, gastroenteritis, granulocytopenia, hot flashes, increased GGT, increased non-protein nitrogen, leg cramps, moniliasis, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, phototoxicity/photosensitivity reactions, pneumonia, thrombocytopenia, tremor, vertigo. (See PRECAUTIONS.)

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

Reference ID: 3356620
Post-Marketing Adverse Reactions: The majority of the post-marketing adverse events reported were cutaneous and most of these were rash. Some of these cutaneous adverse events were considered serious. The majority of the rashes occurred in women and in patients under 40 years of age.

The following are additional adverse reactions reported during the post-marketing use of FACTIVE. Since these reactions are reported voluntarily from a population of uncertain size, it is impossible to reliably estimate their frequency or establish a causal relationship to FACTIVE exposure:

- peripheral neuropathy that may be irreversible;
- anaphylactic reaction, erythema multiforme, skin exfoliation, facial swelling;
- exacerbation of myasthenia gravis;
- hemorrhage, increased international normalized ratio (INR), retinal hemorrhage;
- peripheral edema;
- renal failure;
- prolonged QT, supraventricular tachycardia, syncope, transient ischemic attack;
- photosensitivity/phototoxicity reaction (See PRECAUTIONS);
- antibiotic-associated colitis;
- tendon rupture.

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.

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

INDICATION DOSE / DURATION
Acute bacterial exacerbation of chronic bronchitis One 320 mg tablet daily for 5 days
Community-acquired pneumonia (of mild to moderate severity) One 320 mg tablet daily for 5 days
due to known or suspected S. pneumoniae, H. influenzae, M. pneumoniae, or C. pneumoniae infection One 320 mg tablet daily for 5 days
due to known or suspected MDROSP*, K. pneumoniae, or M. catarrhalis infection One 320 mg tablet daily for 7 days

*MDROSP: 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 (MIC >2 µg/mL), 2nd generation cephalosporins (e.g., cefotaxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

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

Use in 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

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>See Usual Dosage</td>
</tr>
<tr>
<td>≤40</td>
<td>160 mg every 24 hours</td>
</tr>
</tbody>
</table>

Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) should receive 160 mg every 24 hours.

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 44001-321-05
320 mg Unit of Use (CR*) 7’s NDC 44001-321-07

*Child Resistant

Storage
Store at 25ºC (77ºF); excursions permitted to 15º-30ºC (59º-86ºF) [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 behavior or CNS interaction typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the active metabolite of the NSAI, 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
op-634-001
multicenter study comparing FACTIVE 320 mg for five days to FACTIVE 320 mg for seven days
acquired pneumonia were clinically evaluated in a double-blind, randomized, prospective,
hospitalized adults with clinically and radiologically determined mild to moderate community-

Previous clinical studies evaluated the efficacy of FACTIVE in a 7-day treatment of CAP in
adults. This clinical program consisted of three double-blind, randomized, actively-controlled
clinical studies (studies 011, 012, and 049) and one open-label, actively-controlled study (study
061). In addition, two uncontrolled studies (studies 068 and 212) were conducted. Three of the

Community Acquired Pneumonia (CAP)
5 Day Treatment Regimen
To evaluate the safety and efficacy of a 5-day course of FACTIVE, 510 outpatient and
cumulatively and radiologically determined mild to moderate community-
acquired pneumonia were clinically evaluated in a double-blind, randomized, prospective,
multicenter study comparing FACTIVE 320 mg for five days to FACTIVE 320 mg for seven days
(Study OP-634-001).
Clinical success rates in the clinically evaluable population were 95.0% in the 5 day
group and 92.1% in the 7 day group.

Table 7. Clinical Response at Follow-Up (Test of Cure): Study OP-634-001
<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Success Rate % (n/N)</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 068</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTIVE 320 mg x 5 days</td>
<td>86.0 (239/278)</td>
<td>1.2 (-4.7, 7.0)</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID x 7 days</td>
<td>84.8 (240/283)</td>
<td></td>
</tr>
<tr>
<td>Study 070</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTIVE 320 mg x 5 days</td>
<td>93.6 (247/264)</td>
<td>0.4 (-3.9, 4.6)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate 500 mg/125 mg TID x 7 days</td>
<td>93.2 (248/266)</td>
<td></td>
</tr>
<tr>
<td>Study 212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTIVE 320 mg x 5 days</td>
<td>88.2 (134/152)</td>
<td>3.1 (-4.7, 10.7)</td>
</tr>
<tr>
<td>Levofloxacin 500 mg x 7 days</td>
<td>85.1 (126/148)</td>
<td></td>
</tr>
</tbody>
</table>

The microbiological efficacy of the 5-day regimen was documented for pathogens
listed in Table 8 below.

Table 8. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Study
OP-634-001
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Success Rate</th>
<th>5-day</th>
<th>7-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>26/26</td>
<td>100</td>
<td>34/40</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>22/25</td>
<td>88.0</td>
<td>19/20</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>21/22</td>
<td>95.5</td>
<td>18/18</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>17/18</td>
<td>94.4</td>
<td>30/31</td>
</tr>
</tbody>
</table>

7 Day Treatment Regimen
Previous clinical studies evaluated the efficacy of FACTIVE in a 7-day treatment of CAP in
adults. This clinical program consisted of three double-blind, randomized, actively-controlled
clinical studies (studies 011, 012, and 049) and one open-label, actively-controlled study (study
185). In addition, two uncontrolled studies (studies 061 and 287) were conducted. Three of the

Table 9. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7-day
Duration of Treatment
<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Success Rate % (n/N)</th>
<th>Treatment Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTIVE 320 mg x 7 days</td>
<td>88.7 (102/115)</td>
<td>1.1 (-7.3, 9.5)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate 1 g/125 mg TID x 10 days</td>
<td>87.6 (99/113)</td>
<td></td>
</tr>
<tr>
<td>Study 061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTIVE 320 mg x 7 days</td>
<td>91.7 (154/168)</td>
<td>(86.1, 95.2)</td>
</tr>
<tr>
<td>Study 287</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACTIVE 320 mg x 7 days</td>
<td>89.8 (123/147)</td>
<td>(84.9, 94.7)</td>
</tr>
</tbody>
</table>

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 10.

Table 10. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies
with a Fixed 7-day Duration of Treatment
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>102/117</td>
<td>87.2</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>204/226</td>
<td>95.5</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>495/530</td>
<td>90.6</td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>43/455</td>
<td>95.6</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>18/20</td>
<td>90.0</td>
</tr>
<tr>
<td>M. catarrhals</td>
<td>11/12</td>
<td>91.7</td>
</tr>
</tbody>
</table>

7 Day Treatment Regimen of Community-Acquired Pneumonia Due to Multi-Drug
Resistant Streptococcus pneumoniae (MDRSP)
FACTIVE was also effective in the treatment of CAP due to multi-drug resistant Streptococcus
pneumoniae (MDRSP). Of 35 patients with MDRSP treated for 7 days, 29 (82.9%) achieved clinical
and bacteriological success at follow-up. The clinical and bacteriological success for the
35 patients with MDRSP isolates are shown in Table 11.

Table 11. Clinical and Bacteriological Success for 35 Patients Treated with FACTIVE in
CAP Studies with a 7-day Duration of Treatment for MDRSP

<table>
<thead>
<tr>
<th>Screening Susceptibility</th>
<th>Clinical Success</th>
<th>Bacteriological Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin-resistant</td>
<td>15/16</td>
<td>93.8</td>
</tr>
<tr>
<td>2nd generation cephalosporin-resistant</td>
<td>20/22</td>
<td>90.9</td>
</tr>
<tr>
<td>Macrolide-resistant*</td>
<td>24/28</td>
<td>85.7</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole-resistant</td>
<td>23/26</td>
<td>88.5</td>
</tr>
<tr>
<td>Tetracycline-resistant</td>
<td>23/27</td>
<td>77.8</td>
</tr>
</tbody>
</table>

*Macrolide antibiotics tested include clarithromycin and erythromycin

Not all isolates were resistant to all antimicrobials classes tested. Success and
eradication rates are summarized in Table 12 below.

Table 12. Resistant Streptococcus pneumoniae Clinical Success and Bacteriological
Eradication Rates
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Clinical Cure Rate</th>
<th>Bacteriological Eradication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae with MDRSP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistant to 2 antimicrobials</td>
<td>8/11</td>
<td>72.7</td>
</tr>
<tr>
<td>Resistant to 3 antimicrobials</td>
<td>5/7</td>
<td>71.4</td>
</tr>
<tr>
<td>Resistant to 4 antimicrobials</td>
<td>8/9</td>
<td>88.9</td>
</tr>
<tr>
<td>Resistant to 5 antimicrobials</td>
<td>8/8</td>
<td>100</td>
</tr>
<tr>
<td>Bacteremia with MDRSP</td>
<td>3/3</td>
<td>100</td>
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Clinical Safety Study of Rash
To further characterize gemifloxacin-associated rash, which in early clinical studies appeared to be associated with age less than 40 and female gender, a clinical pharmacology study was conducted. The study enrolled 1,101 healthy female volunteers less than 40 years of age. Subjects were randomized in a 5:1 ratio to receive either FACTIVE 320 mg PO daily (819 subjects) or ciprofloxacin 500 mg PO twice daily for 10 days (164 subjects). This study was designed to enroll subjects at a high risk for rash (women <40 years of age and dosing beyond the recommended duration of therapy for FACTIVE [10 days]) and over estimates the risk to patients taking FACTIVE as prescribed. Subjects who received FACTIVE were 7 times more likely to develop rash than those who received ciprofloxacin. Of the 260 rashes in subjects receiving FACTIVE, the majority of rashes 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. Approximately 11% of the rashes were described as being “urticaria-like.” There were no documented cases of hypersensitivity syndrome or findings suggestive of angioedema or other serious cutaneous reactions.

The majority of rashes (81.9%) occurred on days 8 through 10 of the planned 10 day course of FACTIVE; 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 FACTIVE were treated with ciprofloxacin (n=136) or placebo (n=50); 5.9% developed rash when treated with ciprofloxacin and 2.0% developed rash when treated with placebo. The cross sensitization rate to other fluoroquinolones was not evaluated in this clinical study. There was no evidence of subclinical sensitization to FACTIVE on a second exposure (i.e., subjects who had not developed a rash to FACTIVE in the first part of the study were not at higher risk of developing a rash to FACTIVE 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:

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MRS-001-0313-02

MEDICATION GUIDE
FACTIVE® [FAC-tiv]
(gemifloxacin)
320mg Tablets

Read the Medication Guide that comes with FACTIVE® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about FACTIVE?
FACTIVE belongs to a class of antibiotics called fluoroquinolones. FACTIVE can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take FACTIVE.

1. Tendon rupture or swelling of the tendon (tendinitis)
   • Tendon problems can happen in people of all ages who take
   Tendons are tough cords of tissue that connect muscles to bones.
   • Symptoms of tendon problems may include: Pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.

   The risk of getting tendon problems while you take FACTIVE is higher if you:
   • are over 60 years of age
   • are taking steroids (corticosteroids)
   • have had a kidney, heart or lung transplant.

   Tendon problems can happen in people who do not have the above risk factors when they take FACTIVE.

   Other reasons that can increase your risk of tendon problems include:
   • physical activity or exercise
   • kidney failure
   • tendon problems in the past, such as in people with rheumatoid arthritis (RA).

   Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking FACTIVE until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen in other tendons.

   Talk to your healthcare provider about the risk of tendon rupture with continued use of FACTIVE. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.

   Tendon rupture can happen while you are taking or after you have finished taking FACTIVE. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.

   Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
   • hear or feel a snap or pop in a tendon area
   • bruising right after an injury in a tendon area
   • unable to move the affected area or bear weight

   Worsening of myasthenia gravis (a disease which causes muscle weakness). Fluoroquinolones like FACTIVE may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section “What are the possible side effects of FACTIVE?” for more information about side effects.

What is FACTIVE?
FACTIVE is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria in adults 18 years or older. It is not known if FACTIVE is safe and works in children under 18 years of age. Children have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking fluoroquinolone antibiotic medicines.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics including FACTIVE do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking FACTIVE.

Who should not take FACTIVE?
Do not take FACTIVE if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in FACTIVE. Ask your healthcare provider if you are not sure. See the list of ingredients in FACTIVE at the end of this Medication Guide.

What should I tell my healthcare provider before taking FACTIVE?
See “What is the most important information I should know about FACTIVE?”

Tell your healthcare provider about all your medical conditions, including if you:
- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation”
- have low blood potassium (hypokalemia) or magnesium (hypomagnesemia)
- have a slow heart beat (bradycardia)
- have a history of seizures
- have kidney problems. You may need a lower dose of FACTIVE if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if FACTIVE will harm your unborn child.
- are breast-feeding or planning to breast-feed. It is not known if FACTIVE passes into breast milk. You and your healthcare provider should decide whether you will take FACTIVE or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal and dietary supplements. FACTIVE and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:
- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take FACTIVE or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See “What are the possible side effects of FACTIVE?”
- a blood thinner ( warfarin, Coumadin®, Jantoven®)
- a medicine to control your heart rate or rhythm (antiarrhythmics) See “What are the possible side effects of FACTIVE?”
- an anti- psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- probenecid (Probalan, Col-Probenecid)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See “What is the most important information I should know about FACTIVE?”
- Certain medicines may keep FACTIVE from working correctly. Take FACTIVE either 3 hours before or 2 hours after taking these products:
  - an antacid, multivitamin, or other product that contains magnesium, aluminum, iron, or zinc
  - sucrafate (Carafate®)
  - didanosine (Videx®, Videx EC®).

Ask your healthcare provider if you are not sure if any of your medicines are listed above.
Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take FACTIVE?
- Take FACTIVE exactly as prescribed by your healthcare provider.
- Take FACTIVE at about the same time each day.

Reference ID: 3356620
- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat
- faint

**Yellowing of the skin or eyes**
Stop taking FACTIVE and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to FACTIVE (a liver problem).

**Skin rash**
Skin rash may happen in people taking FACTIVE. Stop taking FACTIVE at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to FACTIVE. Rash happens more often with FACTIVE in:
- women, especially women who take hormone replacement therapy
- people under 40 years of age
- people who take FACTIVE for longer than 5 days.

**Serious heart rhythm changes** (QT prolongation and torsades de pointes)
Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. FACTIVE may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:
- who are elderly
- with a family history of prolonged QT interval
- with low blood potassium (hypokalemia)
- who take certain medicines to control heart rhythm (antiarrhythmics).

**Intestine infection** (Pseudomembranous colitis)
Pseudomembranous colitis can happen with most antibiotics, including FACTIVE. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

**Changes in sensation and nerve damage** (peripheral neuropathy)
Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including FACTIVE. Stop FACTIVE and talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
- pain
- burning
- tingling
- numbness
- weakness
The nerve damage may be permanent.

**Sensitivity to sunlight** (photosensitivity)
See “What should I avoid while taking FACTIVE?”

**Joint problems**

The most common side effects of FACTIVE include:
- diarrhea
- rash
- nausea
- headache
- stomach pain
- vomiting
- dizziness

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store FACTIVE?**
- Store FACTIVE at 59º - 86ºF (15º to 30ºC).
- Keep FACTIVE away from light.

**Keep FACTIVE and all medicines out of the reach of children.**

**General Information about FACTIVE**
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FACTIVE for a condition for which it is not prescribed. Do not give FACTIVE to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about FACTIVE. If you would like more information about FACTIVE, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about FACTIVE that is written for healthcare professionals. For more information go to www.FACTIVE.com or call 1-888-431-4276.

**What are the ingredients in FACTIVE?**
- Active ingredient: gemifloxacin
- Inactive ingredients: crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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These are not all the possible side effects of FACTIVE. Tell your healthcare provider about any side effect that bothers you or that does not go away.

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