

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use FACTIVE® safely and effectively. See full prescribing information for FACTIVE®.

FACTIVE® (gemifloxacin mesylate) tablets, for oral use  
Initial U.S. Approval: 2003

**WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATIONS OF MYASTHENIS GRAVIS**  
*See full prescribing information for complete boxed warning.*

- Fluoroquinolones, including FACTIVE, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:

- Tendinitis and tendon rupture(5.2)
- Peripheral neuropathy(5.3)
- Central nervous system effects(5.4)

Discontinue FACTIVE immediately and avoid the use of fluoroquinolones, including FACTIVE, in patients who experience any of these serious adverse reactions. (5.1)

- Fluoroquinolones, including FACTIVE, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid FACTIVE in patients with known history of myasthenia gravis. (5.5)
- Because fluoroquinolones, including FACTIVE, have been associated with serious adverse reactions (5.1-5.11), reserve FACTIVE for use in patients who have no alternative treatment options for acute bacterial exacerbation of chronic bronchitis (ABECB) (1.1).

**INDICATIONS AND USAGE**

FACTIVE® is a fluoroquinolone antibacterial indicated for treatment in adults (18 years of age or older) with the following infections caused by designated, susceptible microorganisms:

- Acute bacterial exacerbation of chronic bronchitis (ABECB). (1.1)
- Community-acquired pneumonia (CAP).(1.2)

Usage

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 (1.3).

**DOSAGE AND ADMINISTRATION**

- Dosage in Adult Patients with a Creatinine Clearance Greater than 40 mL/min (2.1)

Type of Infection	Dose every 24 hours	Duration (days)
Acute bacterial exacerbation of chronic bronchitis (ABECB)	320 mg	5
Community-acquired pneumonia (CAP)	320 mg	5 to 7 days

- Adjust dosage for patients with creatinine clearance less than or equal to 40 mL/min to 160 mg every 24 hours.(2.2, 8.8)

**DOSAGE FORMS AND STRENGTHS**

Tablets: 320 mg (3)

**CONTRAINDICATIONS**

- Known hypersensitivity to FACTIVE or other quinolones (4, 5.7)

**WARNINGS AND PRECAUTIONS**

- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (5.7)
- *Clostridium difficile*-associated Diarrhea: evaluate if diarrhea occurs (5.8)
- Prolongation of the QT interval and isolated cases of torsade de pointes have been reported with FACTIVE. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval (5.9, 8.5)

**ADVERSE REACTIONS**

Most common adverse reactions (incidence 3% or greater) were diarrhea, rash, nausea and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LG Chem at toll-free phone # 1-866-686-6174 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

Interacting Drug	Interaction
Multivalent cation-containing products including antacids, metal cations or didanosine	Decreased FACTIVE absorption when tablets are taken within 2 hours of these products. (7.1)
Warfarin	Monitor prothrombin time, INR, and bleeding (7.9)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal data may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS**

**1 INDICATIONS AND USAGE**

- 1.1 Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)
- 1.2 Community-Acquired Pneumonia
- 1.3 Usage

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Dosage in Adult Patients with Creatinine Clearance Greater than 40 mL/min
- 2.2 Dosage in Adult Patients with Renal Impairment
- 2.3 Dosage Modifications Due to Drug Interactions

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects
- 5.2 Tendinitis and Tendon Rupture
- 5.3 Peripheral Neuropathy
- 5.4 Central Nervous System (CNS) Effects
- 5.5 Exacerbation of Myasthenia Gravis
- 5.6 Other Serious and Sometimes Fatal Adverse Reactions
- 5.7 Hypersensitivity Reactions
- 5.8 Clostridium difficile Associated Diarrhea
- 5.9 Prolongation of the QT Interval
- 5.10 Blood Glucose Disturbances
- 5.11 Photosensitivity Potential
- 5.12 Development of Drug Resistant Bacteria

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

7.1 Antacids/Di- and Trivalent Cations

7.2 Sucralfate

7.3 Warfarin

7.4 Probenecid

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Gender

8.7 Hepatic Impairment

8.8 Renal Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.4 Microbiology

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

14.1 Acute Bacterial Exacerbation of Chronic Bronchitis

14.2 Community Acquired Pneumonia : 5 to 7 day Treatment

14.3 Clinical Safety Study of Rash

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### **WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATIONS OF MYASTHENIS GRAVIS**

- Fluoroquinolones, including FACTIVE<sup>®</sup>, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together including [see *Warnings and Precautions*(5.1)], including:
  - Tendinitis and tendon rupture [see *Warnings and Precautions*(5.2)]:
  - Peripheral neuropathy [see *Warnings and Precautions*(5.3)]:
  - Central nervous system effects [see *Warnings and Precautions*(5.4)]:Discontinue FACTIVE immediately and avoid the use of fluoroquinolones, including FACTIVE, in patients who experience any of these serious adverse reactions [see *Warnings and Precautions* (5.1)]
- Fluoroquinolones, including FACTIVE, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid FACTIVE in patients with known history of myasthenia gravis [see *Warnings and Precautions*(5.5)].
- Because fluoroquinolones, including FACTIVE, have been associated with serious adverse reactions [see *Warnings and Precautions*(5.1-5.11)], reserve FACTIVE for use in patients who have no alternative treatment options for acute bacterial exacerbation of chronic bronchitis [see *Indications and Usage* (1.1)].

## 1 INDICATIONS AND USAGE

### 1.1 Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

FACTIVE is indicated in adult patients (18 years and older) for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis* [see *Clinical Studies* (14.1)].

Because fluoroquinolones, including FACTIVE, have been associated with serious adverse reactions [see *Warnings and Precautions* (5.1-5.11)] and for some patients ABECB is self-limiting, reserve FACTIVE for treatment of ABECB in patients who have no alternative treatment options.

### 1.2 CommunityAcquired Pneumonia

FACTIVE is indicated in adult patients (18 years and older) for the treatment of 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* [see *Clinical Studies* (14.2)].

Multi-drug resistant *Streptococcus pneumoniae* (MDRSP), includes isolates previously known as penicillin-resistant *Streptococcus pneumoniae* (PRSP), and are strains resistant to two or more of the following antibacterial drugs: penicillin (MIC  $\geq 2$   $\mu\text{g/mL}$ ), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

### 1.3 Usage

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 or prevent 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage in Adult Patients with Creatinine Clearance Greater than 40 mL/min

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.

The clinical decision regarding the use of a 5 day or 7day regimen should be guided by results of the initial sputum culture.

**Table 1. Recommended Dosage of FACTIVE in Adult Patients with Creatinine Clearance Greater than 40 mL/min**

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) <i>due to known or suspected S. pneumoniae, H. influenzae, M. pneumoniae, or C. pneumoniae infection</i>	One 320 mg tablet daily for 5 days
<i>due to known or suspected MDRSP*, K. pneumoniae, or M. catarrhalis infection</i>	One 320 mg tablet daily for 7 days

\*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  $\geq 2$   $\mu\text{g/mL}$ ), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

- FACTIVE may be taken with or without meals
- The recommended dose and duration of FACTIVE should not be exceeded (see Table 1).

### 2.2 Dosage in Adult Patients with Renal Impairment

Dose adjustment in adult patients with creatinine clearance greater than 40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance less than or equal to 40 mL/min. Table 2 provides dosage guidelines for use in patients with renal impairment.

**Table 2. Recommended Dosage for Adult Patients with Renal Impairment(Creatinine Clearance equal to or less than 40 mL/min)**

Creatinine Clearance (mL/min)	Dose
Greater than 40	See Usual Dosage
Less than or equal to 40	160 mg every 24 hours

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.

$$\text{Men: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men

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

### 2.3 Dosage Modifications Due to Drug Interactions

#### Antacids/Di- and Trivalent Cations

Aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx<sup>®</sup> (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 [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

#### Sucralfate

Administer FACTIVE at least 2 hours before sucralfate [see *Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)*].

## 3 DOSAGE FORMS AND STRENGTHS

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.

## 4 CONTRAINDICATIONS

FACTIVE is contraindicated in patients with a history of hypersensitivity to gemifloxacin, other fluoroquinolone antibacterial agents, or any of the product components [see *Warnings and Precautions (5.7)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects:

Fluoroquinolones, including FACTIVE have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting FACTIVE. Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue FACTIVE immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including FACTIVE, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

## 5.2 Tendinitis and Tendon Rupture

Fluoroquinolones, including FACTIVE, have been associated with an increased risk of tendinitis and tendon rupture in all ages [see *Warnings and Precautions (5.1) and Adverse Reactions (6.2)*]. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur within hours or days after starting FACTIVE, or as long as several months after completion of therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other 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. Discontinue FACTIVE if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including FACTIVE, in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture. 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 [see *Adverse Reactions (6.2)*].

## 5.3 Peripheral Neuropathy

Fluoroquinolones, including FACTIVE, have been associated with an increased risk of 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 in some patients [see *Warnings and Precautions (5.1) and Adverse Reactions (6.2)*].

Discontinue FACTIVE immediately if the patient experiences symptoms of peripheral neuropathy, including pain, burning, tingling, numbness, and/or weakness or other alterations in sensations including light touch, pain, temperature, position sense, and vibratory sensation.[see *Adverse Reactions (6.2)*]. Avoid fluoroquinolones, including FACTIVE, in patients who have previously experienced peripheral neuropathy [see *Adverse Reactions (6.2)*].

## 5.4 Central Nervous System (CNS) Effects

### Psychiatric Adverse Reactions

Fluoroquinolones, including FACTIVE, have been associated with an increased risk of psychiatric adverse reactions, including toxic psychosis, hallucinations or paranoia; depression, suicidal thoughts or acts; anxiety, agitation, or restlessness; confusion, delirium, disorientation, or disturbances in attention; insomnia; memory impairment. These reactions may occur following the first dose. If these reactions occur in patients receiving FACTIVE, discontinue FACTIVE immediately and institute appropriate measures.

### Central Nervous System Adverse Reactions

Fluoroquinolones, including FACTIVE, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (pseudotumor cerebri), lightheadedness; and tremors. As with other fluoroquinolones, FACTIVE should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. If these reactions occur in patients receiving FACTIVE, discontinue FACTIVE immediately and institute appropriate measures.

*[see Adverse Reactions (6); Drug Interactions (7)].*

## 5.5 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including FACTIVE, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid FACTIVE in patients with known history of myasthenia gravis *[see Adverse Reactions (6.2)]*.

## 5.6 Other Serious and Sometimes Fatal Adverse Reactions

Other serious and sometimes fatal adverse reactions, some due to hypersensitivity and some due to uncertain etiology, have been reported rarely in patients receiving therapy with fluoroquinolones, 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.

Discontinue FACTIVE immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and institute supportive measures *[see Adverse Reactions (6.2)]*.

In clinical studies, rash occurred more often with FACTIVE than with therapy 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. 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%) [see *Adverse Reactions* (6.1)]. Discontinue FACTIVE in patients who develop a rash or urticaria while on treatment.

### 5.7 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 *Adverse Reactions* (6)].

### 5.8 *Clostridium difficile*- Associated Diarrhea

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of 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 antimicrobial therapy 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 [see *Adverse Reactions* (6)].

### 5.9 Prolongation of the QT Interval

FACTIVE has been reported to prolong the QT interval of the electrocardiogram in some patients [see *Adverse Reactions* (6.2)]. 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 FACTIVE 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 C<sub>max</sub> 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 [see *Adverse Reactions (6.2) and Use in Specific Populations (8.5)*].

### **5.10 Blood Glucose Disturbances**

Fluoroquinolones have been associated with disturbances of blood glucose, including symptomatic hyperglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. Severe cases of hypoglycemia resulting in coma or death have been reported from other Fluoroquinolones. If a hypoglycemic reaction occurs in a patient being treated with FACTIVE, discontinue FACTIVE and initiate appropriate therapy immediately.

### **5.11 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 region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg BID and the photosensitivity potential for both drugs were statistically greater than that of placebo. Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin (0.039%).

Moderate to severe photosensitivity/phototoxicity 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 fluoroquinolones, such as FACTIVE, after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. FACTIVE should be discontinued if phototoxicity occurs.

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 therapy [see *Adverse Reactions (6.2)*].

### **5.12 Development of Drug Resistant Bacteria**

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

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects [see *Warnings and Precautions* (5.1)]
- Tendinitis and Tendon Rupture [see *Warnings and Precautions* (5.2)]
- Peripheral Neuropathy [see *Warnings and Precautions* (5.3)]
- CNS Effects [see *Warnings and Precautions* (5.4)]
- Exacerbation of Myasthenia Gravis [see *Warnings and Precautions* (5.5)]
- Other Serious and Sometimes Fatal Adverse Reactions [see *Warnings and Precautions* (5.6)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.7)]
- *Clostridium difficile* Associated Diarrhea [see *Warnings and Precautions* (5.8)]
- Prolongation of the QT Interval [see *Warnings and Precautions* (5.9)]
- Photosensitivity Potential [see *Warnings and Precautions* (5.10)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies, 8119 patients received daily oral doses of 320 mg FACTIVE. In addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of FACTIVE in clinical pharmacology studies.

#### Adverse Reactions Leading to Discontinuation

FACTIVE was discontinued because of an adverse reactions in 2.0% of patients, primarily due to rash (0.8%), nausea (0.3%), diarrhea (0.3%), urticaria (0.2%) and vomiting (0.2%). Comparator antibacterial drugs were discontinued because of an adverse reaction at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.4%), vomiting (0.3%), rash (0.3%), abdominal pain (0.2%) and vertigo (0.2%).

#### Most Commonly Reported Adverse Reactions

The most commonly reported adverse reactions with a frequency of greater than or equal to 2% for patients receiving 320 mg FACTIVE versus comparator drug (beta-lactam antibiotics, macrolides or other fluoroquinolones) are found in Table 3.

**Table 3 Selected Adverse Reactions Occurring in Greater than or Equal to 1% of Patients Receiving FACTIVE versus Comparator Drugs**

Adverse Reactions	FACTIVE	Comparator Drugs
Diarrhea	5.0%	6.2%
Headache	4.2%	5.2%
Nausea	3.7%	4.5%
Rash	3.5%	1.1%
Abdominal pain	2.2%	2.2%
Dizziness	1.7%	2.6%
Vomiting	1.6%	2.0%

Adverse Reactions with a Frequency of Less than 1%

Additional adverse reactions in the 8119 patients, with a frequency of greater than 0.1% to less than or equal to 1% included:

*Blood and Lymphatic System Disorders:* thrombocythemia,

*Gastrointestinal Disorders:* abdominal pain, constipation, dry mouth, dyspepsia, flatulence, gastritis, vomiting

*General Disorders and Administration Site Conditions:* fatigue

*Infections and Infestations:* fungal infection

*Laboratory investigations:* increased alanine aminotransferase, increased aspartate aminotransferase, increased alkaline phosphatase, increased creatine phosphokinase,

*Metabolism and Nutrition Disorders:* anorexia, hyperglycemia,

*Nervous System Disorders:* dizziness, taste perversion,

*Psychiatric Disorders:* insomnia, somnolence

*Reproductive System and Breast Disorders:* genital moniliasis, genital pruritus, vaginitis,

*Skin and Subcutaneous Tissues Disorders:* dermatitis, pruritus, urticarial

Other adverse reactions reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in  $\leq 0.1\%$  of patients were:

*Blood and Lymphatic System Disorders:* anemia, eosinophilia, granulocytopenia, thrombocythemia,

*Ear and Labyrinth Disorders:* vertigo.

*Eye Disorder:* abnormal vision

*Gastrointestinal Disorders:* gastroenteritis, non-specified gastrointestinal disorder

*General Disorders and Administration Site Conditions:* asthenia, facial edema, hot flashes, pain

*Infections and Infestations:* moniliasis, pharyngitis, pneumonia

*Investigations:* abnormal urine, gamma-glutamyltransferase increased, increased non-protein nitrogen

*Metabolism and Nutrition Disorders:* bilirubinemia

*Musculoskeletal and Connective Tissue Disorders:* arthralgia, back pain, leg cramps, myalgia

*Nervous System Disorders:* dizziness, tremor

*Psychiatric Disorders:* insomnia, nervousness, somnolence

*Respiratory, Thoracic and Mediastinal Disorders:* dyspnea

*Skin and Subcutaneous Tissues Disorders:* eczema, flushing, photosensitivity/phototoxicity reactions

## Rash

In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), the incidence of rash were as follows (Table 4):

**Table 4. Incidence of Rash by Clinical Indication in Patients Treated with FACTIVE**

	ABECB (5 days) N = 2284		CAP (5 days) N = 256		CAP (7 days) N = 643	
	n/N	%	n/N	%	n/N	%
Totals	27/2284	1.2	1/256	0.4	26/643	4.0
Females, less than 40 years	NA*		1/37	2.7	8/88	9.1
Females, 40 years and older	16/1040	1.5	0/73	0	5/214	2.3
Males, less than 40 years	NA*		0/65	0	5/101	5.0
Males, 40 years and older	11/1203	0.9	0/81	0	8/240	3.3

\* Insufficient number of patients in this category for a meaningful analysis

In clinical studies, rash occurred more often with FACTIVE than with therapy 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 3). 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.

**Table 5. Rash Incidence in FACTIVE Treated Patients from the Clinical Studies Population\* by Gender, Age, and Duration of Therapy**

Gender & Age (yr) Category	Duration of FACTIVE Therapy			
	5 days	7 days	10 days**	14 days**
<b>Female less than 40 years</b>	10/399 (2.5%)	49/407 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
<b>Female 40 years and older</b>	30/1438 (2.1%)	34/887 (3.8%)	19/308 (6.2%)	10/126 (7.9%)
<b>Male less than 40</b>	6/356 (1.7%)	26/453 (5.7%)	7/74 (9.5%)	3/39 (7.7%)
<b>Male 40 years and older</b>	10/1503 (0.7%)	26/984 (2.6%)	9/345 (2.6%)	3/116 (2.6%)
<b>Totals</b>	56/3696 (1.5%)	135/2732 (4.9%)	55/858 (6.4%)	23/312 (7.4%)

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

\*\*exceeds the recommended duration of therapy [see *Dosage and Administration (2)*]

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 of 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.

### Laboratory Changes

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

Clinical Chemistry: increased ALT (1.7%), increased AST (1.3%), increased creatine phosphokinase (0.7%), increased alkaline phosphatase (0.4%), increased total bilirubin (0.4%), increased potassium (0.3%), decreased sodium (0.2%), increased blood urea nitrogen (0.3%), decreased albumin (0.3%), increased serum creatinine (0.2%), decreased calcium (0.1%), decreased total protein (0.1%), decreased potassium (0.1%), increased sodium (0.1%), increased lactate dehydrogenase (<0.1%) and increased calcium (<0.1%).

CPK elevations were noted infrequently: 0.7% in FACTIVE patients vs. 0.7% in the comparator patients. Hematology: increased platelets (1.0%), 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 FACTIVE treated patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 15% showed a further elevation of their ALT at the on-therapy visit and 9% 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.

In a clinical trial where 638 patients received either a single 640 mg dose of FACTIVE 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.

## **6.2 Postmarketing Experience**

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
- antibiotic-associated colitis;
- tendon rupture.

## 7 DRUG INTERACTIONS

### 7.1 Antacids/Di- and Trivalent Cations

Fluoroquinolones, including FACTIVE, 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 [see *Clinical Pharmacology (12.3)*]. Aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx<sup>®</sup> (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.

### 7.2 Sucralfate

When sucralfate (was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced [see *Clinical Pharmacology (12.3)*]. Therefore, FACTIVE should be taken at least 2 hours before sucralfate.

### 7.3 Warfarin

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 PT, INR or other suitable coagulation test should be closely monitored if a quinolone antimicrobial, including FACTIVE, is administered concomitantly with warfarin or its derivatives

### 7.4 Probenecid

Concomitant administration of FACTIVE with probenecid resulted in an increase in the systemic exposure to gemifloxacin and reduction in the mean renal clearance of gemifloxacin [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The limited available human data with FACTIVE use in pregnant women are insufficient to inform an associated risk of miscarriages, major birth defects, and/or adverse maternal or fetal outcomes.

Based on animal studies with gemifloxacin, FACTIVE, may cause fetal harm. In animal reproduction studies, administration of gemifloxacin to pregnant mice and rabbits during the period of organogenesis produced embryofetal toxicity at exposures up to 2 and 3 times, respectively, the maximum recommended human dose. (see *Data*). Advise pregnant women of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## Data

### *Animal Data*

In animal reproduction studies, gemifloxacin administered orally to pregnant mice (60, 250, or 450 mg/kg/day) from gestation days (GD) 6-15 and intravenously to pregnant rabbits (10, 20, or 40 mg/kg/day) from GD 7-19 resulted in fetal growth retardation, including reduced fetal body weights in mice and rabbits and delayed skeletal ossification in mice at 2 and 3 times, respectively, the clinical exposures (based on AUC).

In a pre/postnatal development study, pregnant rats treated with oral gemifloxacin at doses of 600 mg/kg/day, (approximately 8-times the clinical exposure based on AUC) from GD 6 through lactation day 20 resulted in lowered fetal birth weights and fetal brain and ocular malformations in the presence of maternal toxicity. By lactation day 20, there were no effects on offspring weight. No adverse effects were noted at doses up to 216 mg/kg/day. No significant adverse effects on survival, sexual maturation, or fertility were observed in rats exposed from before birth (in utero) through lactation from gemifloxacin at the highest dose tested.

## **8.2 Lactation**

### Risk Summary

There is no data on the presence of gemifloxacin in human milk, the effects on milk production, or the effects on the breastfed infant. Gemifloxacin is excreted in the breast milk of rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FACTIVE and any potential adverse effects on the breastfed child from FACTIVE or from the underlying maternal condition.

## **8.4 Pediatric Use**

The pharmacokinetics of FACTIVE in pediatric subjects have not been studied.

Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including FACTIVE, cause arthropathy and osteochondrosis in immature animals.

## **8.5 Geriatric Use**

Of the total number of subjects in clinical studies of FACTIVE, 29% (2314) were 65 and over, while 11% (865) were 75 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse reaction 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.

In adult subjects, the pharmacokinetics of FACTIVE are not affected by age.

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, hand, 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.

Elderly 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) [see *Warnings and Precautions* (5.9)].

## 8.6 Gender

There are no significant differences between FACTIVE pharmacokinetics in males and females when differences in body weight are taken into account [see *Clinical Pharmacology* (12.3)].

## 8.7 Hepatic Impairment

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 *Clinical Pharmacology* (12.3)].

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 FACTIVE at doses greater than the recommended dose (i.e., 480 mg per day or greater) there was an increased incidence of elevations in liver enzymes. There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy.

## 8.8 Renal Impairment

Dose adjustment in patients with creatinine clearance greater than 40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance less than or equal to 40 mL/min [see *Dosage and Administration* (2.2)]. 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 [see *Clinical Pharmacology* (12.3)].

## 10 OVERDOSAGE

Any signs or symptoms of overdose should be treated symptomatically. No specific antidote is known. In the event of acute oral overdose, 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.

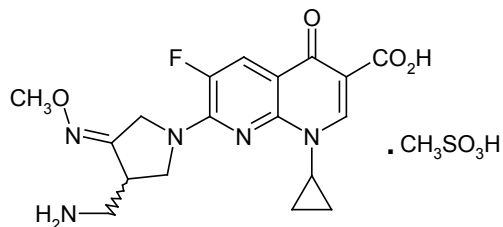
Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400 mg/kg) of gemifloxacin to rodents included ataxia, lethargy,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

## 11 DESCRIPTION

FACTIVE (gemifloxacin mesylate) is a synthetic 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-pyrrolidiny]-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<sub>18</sub>H<sub>20</sub>FN<sub>5</sub>O<sub>4</sub>•CH<sub>4</sub>O<sub>3</sub>S 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.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

FACTIVE is a member of the fluoroquinolone class of antibacterial agents [see *Microbiology (12.4)*].

### 12.3 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. Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (C<sub>max</sub>) 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).

#### Absorption

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%).

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  $V_{dss}/F$  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 6.

**Table 6. Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)**

<b>Tissue</b>	<b>Concentration (mean ± SD)</b>	<b>Ratio compared with plasma (mean ± SD)</b>
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)

### Elimination

The mean plasma elimination half-life at steady state following 320 mg to healthy subjects was approximately 7± 2 hours (range 4-12 hours).

### *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*

Following oral administration of gemifloxacin to healthy subjects, a mean (%SD) of 61± 9.5% of the dose was excreted in feces and 36± 9.3% in 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.

### Specific Populations

#### *Male and Female Patients*

Population pharmacokinetic studies indicated that following administration of 320 mg FACTIVE, 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  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ), respectively. No FACTIVE dosage adjustment based on gender is necessary.

#### *Patients with Hepatic Impairment*

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 C<sub>max</sub> 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 C<sub>max</sub> 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 [see *Use in Specific Populations* (8.7)].

#### *Patients with Renal Impairment*

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 impairment. In the pharmacokinetic studies, gemifloxacin C<sub>max</sub> was not significantly altered in subjects with renal impairment [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.8)]. Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

#### Drug Interaction Studies

*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%; C<sub>max</sub> 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. 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 C<sub>max</sub> decreased] [see *Dosage and Administration* (2.4) and *Drug Interactions* (7.1)].

#### 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 C<sub>max</sub>). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected [see *Dosage and Administration* (2.4) and *Drug Interactions* (7.2)].

#### *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/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 C<sub>max</sub> 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/levonorgestrol oral contraceptive product (30 µg/150 µg once daily for 21 days to healthy female subjects).

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

### *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 C<sub>max</sub> 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 C<sub>max</sub> 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).

### *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 C<sub>max</sub> increased 8%.

## **12.4 Microbiology**

### Mechanism of Action

Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs).

### Resistance

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 to gemifloxacin is low ( $10^{-7}$  to  $<10^{-10}$ ). *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.

### Cross Resistance

Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin. 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.

### Antimicrobial Activity

Gemifloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

### **Aerobic bacteria**

#### **Gram-positive bacteria**

*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  $\geq 2$   $\mu\text{g/mL}$ ), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

#### **Gram-negative bacteria**

*Haemophilus influenzae*

*Haemophilus parainfluenzae*

*Klebsiella pneumoniae*

*Moraxella catarrhalis*

#### **Other microorganisms**

*Chlamydia pneumoniae*

*Mycoplasma pneumoniae*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimal inhibitory concentrations (MIC) less than or equal to the susceptible breakpoint for gemifloxacin against isolates of similar genus or organism group. However, the efficacy of gemifloxacin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials:

### **Aerobic bacteria**

#### **Gram-positive bacteria**

*Staphylococcus aureus* (methicillin-susceptible strains only)

*Streptococcus pyogenes*

### **Gram-negative bacteria**

*Acinetobacter lwoffii*

*Klebsiella oxytoca*

*Legionella pneumophila*

*Proteus vulgaris*

### Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see <https://www.fda.gov/STIC>.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 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 C<sub>max</sub> 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.

## 13.2 Animal Toxicology and/or Pharmacology

### 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 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 C<sub>max</sub>, and transient prolongation after intravenous administration at more than 4 times human plasma levels at C<sub>max</sub>. Gemifloxacin exhibited weak activity in the cardiac IK<sub>r</sub> (hERG) channel inhibition assay, having an IC<sub>50</sub> 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.

## 14 CLINICAL STUDIES

### 14.1 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 7](#) below.

**Table 7. Clinical Response at Follow-Up (Test of Cure): Pivotal ABECB Studies**

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

## 14.2 Community Acquired Pneumonia (CAP): 5 to 7 day Treatment

### 5 Day Treatment Regimen

To evaluate the safety and efficacy of a 5-day course of FACTIVE, 510 outpatient and hospitalized adults with clinically 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 8. Clinical Response at Follow-Up (Test of Cure): Study OP-634-001**

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)
<b>Study OP-634-001</b>		
FACTIVE 320 mg x 5 days	95.0 (230/242)	3.0 (-1.5, 7.4)
FACTIVE 320 mg x 7 days	92.1 (209/227)	

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

**Table 9. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Study OP-634-001**

Pathogen	5-day		7-day	
	n/N	%	n/N	%
<i>Streptococcus pneumoniae</i>	26/26	100	34/40	85.0
<i>Mycoplasma pneumoniae</i>	22/25	88.0	19/20	95.0
<i>Haemophilus influenzae</i>	21/22	95.5	18/18	100
<i>Chlamydia pneumoniae</i>	17/18	94.4	30/31	96.8

### 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 studies, controlled study 011 and the uncontrolled studies, had a fixed 7-day duration of treatment for FACTIVE. Controlled 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 of FACTIVE are shown in Table 10.

**Table 10. Clinical Response at Follow-Up (Test of Cure): CAP Studies with a Fixed 7-day Duration of Treatment**

Drug Regimen	Success Rate % (n/N)	Treatment Difference (95% CI)*
<b>Study 011</b>		
FACTIVE 320 mg x 7 days	88.7 (102/115)	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 1 g/125 mg TID x 10 days	87.6 (99/113)	
<b>Study 061</b>		
FACTIVE 320 mg x 7 days	91.7 (154/168)	(86.1, 95.2)
<b>Study 287</b>		
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 11.

**Table 11. Bacterial Eradication by Pathogen for Patients Treated with FACTIVE in Studies with a Fixed 7-day Duration of Treatment**

Pathogen	n/N	%
<i>S. pneumoniae</i>	102/117	87.2
<i>M. pneumoniae</i>	40/42	95.2
<i>H. influenzae</i>	48/53	90.6
<i>C. pneumoniae</i>	43/45	95.6
<i>K. pneumoniae</i>	18/20	90.0
<i>M. catarrhalis</i>	11/12	91.7

**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 12.

\*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  $\geq$  2 $\mu$ g/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

**Table 12. Clinical and Bacteriological Success for 35 Patients Treated with FACTIVE in CAP Studies with a 7-day Duration of Treatment for MDRSP**

Screening Susceptibility	Clinical Success		Bacteriological Success	
	n/N <sup>a</sup>	%	n/N <sup>b</sup>	%
Penicillin-resistant	15/16	93.8	15/16	93.8
2 <sup>nd</sup> generation cephalosporin-resistant	20/22	90.9	20/22	90.9
Macrolide-resistant <sup>c</sup>	24/28	85.7	23/28	82.1
Trimethoprim/sulfamethoxazole-resistant	23/26	88.5	23/26	88.5
Tetracycline-resistant	21/27	77.8	20/27	74.1

<sup>a</sup>n = the number of patients successfully treated; N = number of patients with MDRSP

<sup>b</sup>n = the number of bacteriological isolates successfully treated; N = number of isolates studied

<sup>c</sup>Macrolide antibiotics tested include clarithromycin and erythromycin

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 13 below.

**Table 13. Resistant *Streptococcus pneumoniae* Clinical Success and Bacteriological Eradication Rates**

<i>S. pneumoniae</i> with MDRSP	Clinical Cure Rate		Bacteriological Eradication Rate	
	n/N	%	n/N	%
Resistant to 2 antimicrobials	8/11	72.7	7/11	63.6
Resistant to 3 antimicrobials	5/7	71.4	5/7	71.4
Resistant to 4 antimicrobials	8/9	88.9	8/9	88.9
Resistant to 5 antimicrobials	8/8	100	8/8	100
Bacteremia with MDRSP	3/3	100	3/3	100

### 14.3 Clinical Safety Study of Rash

To further characterize FACTIVE-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 1,011 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 less than 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, greater than 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. A pproximately 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 sub-clinical 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 (C<sub>max</sub> and AUC) to either gemifloxacin or its major metabolite, N-acetyl gemifloxacin.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 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 (5 Tablets)	NDC 44001-321-05
320 mg Unit of Use (7 Tablets)	NDC 44001-321-07

Tablets are enclosed in a child-resistant package.

### Storage

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Serious Adverse Reactions

Advise patients to stop taking FACTIVE if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug.

Inform patients of the following serious adverse reactions that have been associated with FACTIVE or other fluoroquinolone use:

- *Disabling and potentially irreversible serious adverse reactions that may occur together.* Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of FACTIVE and may occur together in the same patient. Inform patients to stop taking FACTIVE immediately if they experience an adverse reaction and to call their healthcare provider;
- *Tendinitis and tendon rupture.* Instruct patients 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;

- *Peripheral neuropathies*: Inform patients that peripheral neuropathies have been associated with the use of FACTIVE, 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;
- *Central nervous system effects* (for example, convulsions, dizziness, lightheadedness, increased intracranial pressure): Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including FACTIVE. Patients should notify their physician before taking FACTIVE if they have a history of convulsions, seizures, or epilepsy; Inform patients that other central nervous system problems such as tremors, restlessness, lightheadedness, confusion and hallucinations may occur rarely;
- *Exacerbation of Myasthenia Gravis*: Inform patients 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;
- *Hypersensitivity Reactions*: Inform patients 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; Inform patients 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;
- *Diarrhea*: Inform patients that diarrhea has been reported in patients with use of nearly all antibacterial agents, including FACTIVE. Diarrhea usually ends when the antibacterial drug 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;
- *Prolongation of the QT interval*: Inform patients of the following:
  - 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
- *Photosensitivity/Phototoxicity*: Inform patients that photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors while using fluoroquinolones, 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.

- *Blood Glucose Disturbances*: Inform the patients that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue FACTIVE and consult a physician.

### Administration with Food, Fluids, and Concomitant Medications

Advise Patients:

- that FACTIVE may be taken with or without meals;
- 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 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 that will be taken concurrently with FACTIVE, including over-the-counter medications and dietary supplements;
- pediatric powder for oral solution within 3 hours before or 2 hours

### Antibacterial Resistance

Patients should be counseled 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 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 and will not be treatable by FACTIVE or other antibacterial drugs in the future.

© Merus Labs International, Inc.  
FACTIVE is a registered trademark of LG Chem.

Manufactured for:



Toronto, ON M5K 1H1 CANADA  
Licensed from LG Chem, Ltd. Seoul, Korea

MRS-001-0313-03

**MEDICATION GUIDE**  
**FACTIVE® (FAC-tiv)**  
**(gemifloxacin mesylate)**  
**tablets, for oral use**

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, a fluoroquinolone antibiotic medicine, can cause serious side effects. Some of these serious side effects can happen at the same time and could result in death.

If you get any of the following serious side effects while you are taking FACTIVE, **you should stop taking FACTIVE immediately and get medical help right away.**

- 1. Tendon rupture or swelling of the tendon (tendinitis). Tendon problems can happen in people of all ages who take FACTIVE.** 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 can include:**
    - physical activity or exercise
    - kidney failure
    - tendon problems in the past, such as in people with rheumatoid arthritis (RA)
  - **Stop taking FACTIVE immediately and get medical help 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 with other tendons.
  - **Talk to your healthcare provider about the risk of tendon rupture with continued use of FACTIVE.** You may need a different antibiotic medicine 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 can happen within hours or days of taking FACTIVE and 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 put weight on the affected area
- 2. Changes in sensation and possible nerve damage (Peripheral Neuropathy).** Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including FACTIVE. Stop taking FACTIVE and call 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
  - weaknessThe nerve damage may be permanent.
- 3. Central Nervous System (CNS) effects.** Seizures have been reported in people who take fluoroquinolone antibiotic medicines, including FACTIVE. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking FACTIVE will change your risk of having a seizure. CNS side effects may happen as soon as after taking the first dose of FACTIVE. Call your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:
  - feel dizzy
  - seizures
  - hear voices, see things, or sense things that are not there (hallucinations)
  - feel restless
  - tremors
  - feel anxious or nervous
  - confusion
  - depression
  - trouble sleeping
  - feel more suspicious (paranoia)
  - suicidal thoughts or acts
  - nightmares
  - feeling lightheaded
- 4. 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. Tell your healthcare provider if you have a history of myasthenia gravis before you start taking FACTIVE. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

**See “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. These bacterial infections include:

- Acute bacterial exacerbation of chronic bronchitis (ABECB)
- Community-acquired pneumonia (CAP)

FACTIVE should not be used in patients with ABECB if there are other treatment options available.

It is not known if FACTIVE is safe and effective 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. Antibiotic medicines 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 medicine 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 end of this Medication Guide for a complete list of ingredients in FACTIVE.

**What should I tell my healthcare provider before taking FACTIVE?**

See **“What is the most important information I should know about FACTIVE?”**

**Before taking FACTIVE, tell your healthcare provider about all your medical conditions, including if you:**

- have tendon problems. FACTIVE should not be used in patients who have a history of tendon problems.
- have a disease that causes muscle weakness (myasthenia gravis). FACTIVE should not be used in patients who have a known history of myasthenia gravis.
- have CNS problems (such as epilepsy).
- have nerve problems. FACTIVE should not be used in patients who have a history of nerve problems called peripheral neuropathy.
- have or have anyone in your family who has an irregular heartbeat, especially a condition called “QT prolongation”.
- have low blood potassium (hypokalemia) or low 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 history of other joint problems.
- are pregnant or planning to become pregnant. It is not known if FACTIVE will harm your unborn child.
- are breastfeeding or planning to breastfeed. It is not known if FACTIVE passes into breast milk. You and your healthcare provider should decide whether you will take FACTIVE or breastfeed.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter 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:**

- a Non-Steroidal Anti-Inflammatory Drug (NSAID). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take FACTIVE or other fluoroquinolones may increase your risk of CNS effects and seizures. See **“What is the most important information I should know about 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 at least 3 hours before or 2 hours after taking these products:

- an antacid, multivitamin, or other product that contains magnesium, aluminum, iron, or zinc
- sucralfate (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.

- FACTIVE tablets should be swallowed.
- FACTIVE can be taken with or without food.
- Drink plenty of fluids while taking FACTIVE.
- Do not skip any doses, or stop taking FACTIVE even if you begin to feel better, until you finish your prescribed treatment, unless:
  - you have tendon effects (see “**What is the most important information I should know about FACTIVE?**”),
  - you have nerve problems (see “**What is the most important information I should know about FACTIVE?**”),
  - you have CNS problems (see “**What is the most important information I should know about FACTIVE?**”),
  - you have a serious allergic reaction (see “**What are the possible side effects of FACTIVE?**”), or
  - your healthcare provider tells you to stop.This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to FACTIVE. If this happens, FACTIVE and other antibiotic medicines may not work in the future.
- If you take too much FACTIVE, call your healthcare provider or get medical help immediately.

**What should I avoid while taking FACTIVE?**

- FACTIVE can make you feel dizzy and lightheaded. **Do not** drive, operate machinery, or do other activities that require mental alertness or coordination until you know how FACTIVE affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. FACTIVE can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking FACTIVE, call your healthcare provider right away. You should use sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

**What are the possible side effects of FACTIVE?**

**FACTIVE may cause serious side effects, including:**

- See “**What is the most important information I should know about FACTIVE?**”
- **Serious allergic reactions.** Allergic reactions can happen in people taking fluoroquinolones, including FACTIVE, even after only 1 dose. Stop taking FACTIVE and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - 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).
  - throat tightness, hoarseness
  - rapid heartbeat
  - faintSkin rash may also 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
- **Clostridium difficile-associated diarrhea (CDAD).** CDAD is an infection of your intestines (bowels) that can happen with many antibiotic medicines like FACTIVE and may cause mild diarrhea to life-threatening swelling of your intestines (colitis). Call your healthcare provider right away if you get stomach cramps, fever, watery diarrhea, diarrhea that does not go away, or bloody stools. CDAD can happen 2 or more months after you have finished your antibiotic medicine.
- **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) or low magnesium (hypomagnesemia)
  - who take certain medicines to control heart rhythm (antiarrhythmics)
- **Changes in blood sugar**  
People who take fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia). Follow your healthcare provider’s instructions for how often to check your blood sugar. If you have diabetes and you get low blood sugar while taking FACTIVE, stop taking FACTIVE and call your healthcare provider right away. Your antibiotic medicine may need to be changed.
- **Sensitivity to sunlight (photosensitivity).** See “**What should I avoid while taking FACTIVE?**”

The most common side effects of FACTIVE include:

- diarrhea
- stomach pain

- rash
- nausea
- headache

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.

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 room temperature between 68°F to 77°F (20°C to 25°C).
- Keep FACTIVE away from light.

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

#### **General Information about the safe and effective use of 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 was 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 health professionals.

#### **What are the ingredients in FACTIVE?**

- **Active ingredient:** gemifloxacin
- **Inactive ingredients:** crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

© Merus Labs International, Inc.

FACTIVE is a registered trademark of LG Chem.

Manufactured for:



Toronto, ON M5K 1H1 CANADA

Licensed from LG Chem, Ltd. Seoul, Korea

MRS-001-0313-03

For more information, go to [www.FACTIVE.com](http://www.FACTIVE.com) or call 1-888-431-4276.

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

Revised 12/2018

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

DMITRI IARIKOV  
12/13/2018