Factive® 320mg
Gemifloxacin Mesylate Film-Coated Tablet

1. NAME OF THE MEDICINAL PRODUCT
Factive Film-coated tablet 320 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin.

3. PHARMACEUTICAL FORM
A white to off-white oval-shaped film-coated tablet with breaklines on both faces debossed with LG 320 on both faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Factive is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

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 pneumonia, or Klebsiella pneumonia.*

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Factive and other antibacterial drugs, Factive should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy, In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Dosage and administration
Factive can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of Factive is 320 mg daily, according to following indication.
Table1. Recommended Dosage Regimen of Factive

Indication	**Dose and Duration**
Pneumonia (Community Acquired Pneumonia)	
-due to known or suspected *S. pneumoniae, H. influenzae, M. pneumoniae, or C. pneumoniae infection*	One tablet once daily for 5 days.
-due to known or suspected *MDRSP, K. pneumoniae, or M. catarrhalis infection*	One tablet once daily for 7 days.

Table below provide dosage guidelines for use in renal impaired patients.

	Creatinine Clearance (ml/min)	**Dosage Regimen**
Mild to moderate renal impairment patient	≥ 40	Follow standard dosage regimen.
Severe renal impairment patient, haemodialysis patients and continuous ambulatory peritoneal dialysis (CAPD) patients	< 40	Take 160 mg once daily.

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

Other special populations
Dosage adjustment in elderly patients or patients with hepatic impairment is not required.

4.3 Contraindications
1) Known hypersensitivity to Factive®, other fluoroquinolones, or any of the product components
2) Patients with a history of Factive® or other fluoroquinolone-associated tendonitis and tendon rupture
3) Children or growing adolescents under 18 years of age
4) Pregnant or lactating women

4.4 Warnings
The use of gemifloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see section Adverse Effects/Undesirable Effects). Treatment of these patients with gemifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

1) Aortic aneurysm and dissection: Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk

assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

2) Prolonged, Disabling and Potentially Irreversible Serious Adverse Drug Reactions: Very rare cases of prolonged (continuing months or year), disabling and potentially irreversible serious adverse reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors.

   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 (See WARNINGS, Tendinitis and Tendon Rupture, Peripheral Neuropathy and Central Nervous System Effects). Factive should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice. In addition, avoid the use of fluoroquinolones, including Factive, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

3) Tendinitis and tendon rupture: Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Factive should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

4) Peripheral Neuropathy: Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Factive should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop

in order to prevent the development of potentially irreversible condition. (see section Adverse Effects/Undesirable Effects).

5) CNS Effects: Fluoroquinolones, including Factive, have been associated with an increased risk of central nervous system (CNS) effects, including convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis. In clinical studies with Factive, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, Factive should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving Factive, discontinue Factive immediately and institute appropriate measures.

6) Exacerbation of Myasthenia Gravis: Fluoroquinolones, including Factive, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid Factive in patients with known history of myasthenia gravis.

7) THE SAFETY AND EFFECTIVENESS OF FACTIVE IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED.

8) QT Effects: Fluoroquinolones may prolong the QT interval in some patients. Factive should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected electrolyte disorders (hypokalemia or hypomagnesemia), and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.
Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Factive should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Factive treatment in over 8119 patients, including 707 patients concurrently receiving drugs known to prolong the QTc interval and 7 patients with hypokalemia.
The likelihood of QTc prolongation may increase with increasing dose of the drug; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades

de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours following oral administration of gemifloxacin.

9) 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.

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

   The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.

10) *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.

11) Retinal detachment (RD)
Some observational studies reported that using fluoroquinolones, including FACTIVE® have been associated with an increased risk of RD. Patients should be advised to consult an ophthalmologist immediately if visual disturbances occur.

12) Fluoroquinolones have been associated with blood glucose disturbances, including symptomatic hyperglycemia or hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent 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 a patient being treated with FACTIVE®, the drug should be discontinued and initiate appropriate therapy immediately.

13) Glucose-6-Phosphate-dehydrogenase (G6PD) Deficiency
Fluoroquinolones have been associated with drug-induced hemolysis in patients with G6PD deficiency. FACTIVE® should be used with caution in patients with G6PD deficiency or patient with positive family history of G6PD deficiency.

14) Heart Valve Regurgitation/Incompetence
Fluoroquinolones have been associated with an increased risk of mitral and aortic regurgitation. FACTIVE® should be used after careful benefit-risk assessment and consideration of other therapeutic options in patients at risk for heart valve regurgitation/incompetence, or in presence of other risk factors or conditions predisposing for heart valve regurgitation/incompetence include congenital or preexisting heart valve disease, connective tissue disorders (e.g., Marfan syndrome or Ehlers-Danlos syndrome), Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis, and infective endocarditis. Patients should be advised to seek immediate medical attention in case of acute dyspnea, new onset of heart palpitations, or development of edema of the abdomen or lower extremities.

15) Photosensitivity Reaction
Fluoroquinolones, including FACTIVE® have been associated with 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) after sun or UV light exposure. Excessive

exposure to these sources of light should be avoided. Discontinue FACTIVE® if phototoxicity (e.g., skin eruption) occurs.

4.5 Precautions

1) General: Prescribing Factive in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
2) Rash: 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 2). Urticarial reactions, some of which were not classified as rash, were more common in Factive patients than in comparator patients (0.6% vs. 0.2%). Factive should be discontinued in patients developing a rash or urticaria while on treatment.

Table2. 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****
Female < 40	10/399 (2.5%)	49/407 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥ 40	30/1438 (2.1%)	34/887 (3.8%)	19/308 (6.2%)	10/126 (7.9%)
Male < 40	6/356 (1.7%)	26/453 (5.7%)	7/74 (9.5%)	3/39 (7.7%)
Male ≥ 40	10/1503 (0.7%)	26/984 (2.6%)	9/345 (2.6%)	3/116 (2.6%)
Totals	56/3696 (1.5%)	135/2732 (4.9%)	55/858 (6.4%)	23/312 (7.4%)

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

**exceeds the recommended duration of therapy

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.

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 quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs.

3) Hepatic Effects: Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving Factive 320 mg daily relative to comparator antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil, amoxicillin/clavulanate potassium, and ofloxacin). In patients who received gemifloxacin at doses of 480 mg per day or greater there was an increased incidence of elevations in liver enzymes.
   There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy. The recommended dose of Factive 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded.
4) Renal Effects: Alteration of the dosage regimen is necessary for patients with impairment of renal function (creatinine clearance ≤40 mL/min). Adequate hydration of patients receiving Factive should be maintained to prevent the formation of a highly concentrated urine.
5) Information for Patients
   Advice the patient to read the Consumer Medication Information Leaflet (RiMUP).

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, 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 is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible;
- 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 quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician

6) Other Information

Advise Patients:

- that increases of the International Normalized Ratio (INR), or prothrombin time (PT), and/or clinical episodes of bleeding have been noted with concurrent administration of warfarin or its derivatives, and Factive. Patients should notify their physicians if they are taking warfarin or its derivatives;
- to inform their physician of any other medications when taken concurrently with Factive, including over-the-counter medications and dietary supplements;
- that Factive may be taken with or without meals;
- to drink 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 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.

4.6 Interaction with other medicinal products and other forms of interaction

1) Antacids/Di- and Trivalent Cations: The absorption of oral gemifloxacin is significantly reduced and its efficacy may be lowered when aluminium- and/or magnesium containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations (e.g., iron and calcium) are concomitantly administered. FACTIVE® should not be taken within three hours before or two hours after taking these agents.
2) Didanosine: FACTIVE® should not be taken within three hours before or two hours after taking didanosine.

3) Sucralfate: The oral bioavailability of gemifloxacin is significantly reduced when sucralfate is administered three hours prior to gemifloxacin. FACTIVE® should be taken at least two hours before sucralfate.
4) Warfarin: FACTIVE® had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy. However, increases in the INR (International Normalized Ratio), or PT (prothrombin time), and/or clinical episodes of bleeding in patients have been noted with the use of quinolones, including FACTIVE®, and warfarin, or its derivatives. 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.
5) Probenecid: Concomitant administration of FACTIVE® with probenecid resulted in the systemic exposure to gemifloxacin and reduction in the mean renal clearance of gemifloxacin.
6) No clinically significant interactions have been observed when gemifloxacin was coadministered with omeprazole, theophylline, digoxin, oral contraceptives, or cimetidine.

4.7 Pregnancy and lactation

1) Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing at 450 mg/kg/day), rats (oral dosing at 750 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day). Treatment of pregnant rats at 750 mg/kg/day caused fetal brain and ocular malformations (unilateral microphthalmia, anophthalmia, and dome shaped head) in the presence of maternal toxicity.
2) Factive should not be used in pregnant women because the safety of Factive in pregnant women has not been established.
3) Stop breast-feeding during the administration of Factive because animal studies have shown gemifloxacin-related material is excreted in the breast milk of rats.

4.8 Pediatric Use

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

4.9 Geriatric Use

In clinical studies of FACTIVE®, no significant differences in safety and effectiveness was observed between geriatric subjects and younger subjects. 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.

Epidemiologic studies reported an increased rate of aortic aneurysm/dissection within two months following use of fluoroquinolones, particularly in elderly patients. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

4.10 Effects on ability to drive and use machines

CNS effects have been seen rarely in clinical trials with Factive. However, as with all drugs, patients should observe their reaction to Factive and, if affected, should no drive or operate machinery.

4.11 Undesirable effects

Clinical Trials Experience

In clinical studies, 8,119 patients received daily oral doses of 320 mg FACTIVE®. In addition, 1,797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of FACTIVE® in clinical pharmacology studies.

Adverse Events with a Frequency of Greater than or Equal to 1%

The most commonly reported adverse events for patients receiving FACTIVE® were diarrhea (5.0%), headache (4.2%), nausea (3.7%), rash (3.5%), abdominal pain (2.2%), dizziness (1.7%), and vomiting (1.6%).

Adverse Events with a Frequency of Less than 1%

Additional adverse events in the 8,119 patients 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 (ALT), increased aspartate aminotransferase (AST), increased alkaline phosphatase (ALP), increased creatinine phosphokinase (CPK);

Metabolism and Nutrition Disorders: Anorexia, hyperglycemia;

****Nervous System Disorders:*** Dizziness, taste perversion;

****Psychiatric Disorders:*** Insomnia, somnolence;

Reproductive System and Breast Disorders: Moniliasis genital, genital pruritus, vaginitis;

Skin and Subcutaneous Tissues Disorders: Dermatitis, pruritus, urticarial.

Other adverse reactions considered to have a suspected relationship to the drug that occurred in ≤0.1% of patients included:

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;

Laboratory investigations: Abnormal urine, gamma-glutamyltransferase (GGT) increased, increased non-protein nitrogen (NPN);

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.

**Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warnings and Precautions).*

Post-Marketing 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.

Post-Marketing Surveillance
Post-marketing surveillance of FACTIVE® conducted in 3,972 patients over the past 6 years in Korea, occurrence rate of adverse events was reported to be 0.9% (34 patients/3,972 patients). The reported adverse events include eight cases of upper abdominal pain (0.2%) and rash (0.2%) respectively, five cases of nausea (0.1%), four cases of urticaria (0.1%), three cases of pruritus (0.1%), two cases of headache (0.1%) and dizziness (0.1%) respectively, and nine individual cases of myalgia, vomiting, constipation, diarrhea, dyspepsia, stomatitis, chest pain, insomnia, and otomycosis. All adverse events and their relationship to the drug cannot be entirely excluded. Among the reported adverse events, serious adverse event includes a single case of generalized rash and unexpected adverse reactions include five individual cases of myalgia, chest pain, abdominal distress, stomatitis, and otomycosis.

Post-Marketing Spontaneous Reporting
Following adverse events have been additionally reported during post-marketing use of FACTIVE®. Since these events are reported spontaneously from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Peripheral neuropathy that may be irreversible;
- Anaphylactic reaction, erythema multiforme, skin exfoliation, facial swelling, pharyngeal swelling, Peripheral edema;
- Exacerbation of myasthenia gravis;
- Hemorrhage Increase of International Normalization Rate (INR), retinal hemorrhage;
- Renal failure;

- Prolonged QT, supraventricular tachycardia, syncope, transient ischemic attack;
- Photosensitivity/phototoxicity reaction;
- Antibiotic-associated colitis;
- Tendon rupture.

4.12 Overdose
In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage; the patient should be carefully observed and treated symptomatically. Adequate hydration should be maintained and hemodialysis does not remove gemifloxacin sufficiently to be useful in overdosage. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
General Properties
Gemifloxacin is a synthetic antibacterial agent (ATC code: J01MA fluoroquinolone class). Gemifloxacin is a fluoroquinolone antibiotic with a wide range of Gram-positive and Gram-negative pathogens.

Mode of Action
The mode of action is by inhibiting DNA synthesis through the inhibition of both bacterial DNA gyrase and topoisomerase. Gemifloxacin is highly selective for bacterial rather than human topoisomerase II, having strong affinity for bacterial topoisomerases II (DNA gyrase) and IV, which are essential enzymes that play a decisive part in the replication, transcription and repair of bacterial DNA.

Susceptible Micro-organisms
- ***Aerobic Gram-positive***

Streptococcus pneumoniae (including multi-drug resistant strains MDRSP*)
Streptoccocus pyogenes (including macrolide resistant)
Streptococcus viridans
Streptococcus agalactiae
Streptococcus milleri
Streptococcus anginosius
Streptococcus constellatus
Streptococcus mitis
etc., Streptococcus species
Staphylococcus aureus (methicillin sensitive)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Staphylococcus haemolyticus
etc., Staphylococcus species
Enterococcus faecalis
Enterococcus faecium

etc., Enterococcus species

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

● ***Aerobic Gram-negative***
Haemophilus influenzae (beta lactamase positive and negative)
Haemophilus parainfluenzae
etc., Haemophilus species
Moraxella catarrhalis (beta lactamase positive and negative)
etc., Moraxella species
Klebsiella pneumoniae
Klebsiella oxytoca
etc., Klebsiella species
Escherichia coli
Neisseria gonorrhoeae
etc., Neisseria species
Acinetobacter lwoffi
Acinetobacter anitratus
Acinetobacter calcoaceticus
Acinetobacter haemolyticus
etc., Acinetobacter species
Citrobacter freundii
Citrobacter koseri
etc., Citrobacter species
Salmonella species
Shigella species
Enterobacter cloacae
Enterobacter aerogenes
etc., Enterobacter species
Serratia marcescens
etc., Serratia species
Proteus mirabilis
Proteus vulgaris
etc., Proteus species
Providencia species
Morganella morganii
etc., Morganella species
Yersinia species
Pseudomonas aeruginosa

etc., Pseudomonas species
Bordetella pertussis
etc., Bordetella species

● ***Atypicals***
Coxiella burnetti
etc., Coxiella species
Mycoplasma pneumoniae
etc., Mycoplasma species
Legionella pneumophila
etc., Legionella species
Chlamydia pneumoniae
etc., Chlamydia species

● ***Anaerobes***
Peptostreptococcus species
Clostridium non-perfringens
Clostridium perfringens
etc., Clostridium species
Fusobacterium species
Porphyromonas species
Prevotella species

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

Absorption and Bioavailability
Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (C_{max}) and systemic drug exposure (AUC (0-24)) were 1.61 ± 0.51 μg/mL (range 0.70-2.62 μg/mL) and 9.93 ± 3.07 μg•hr/mL (range 4.71-20.1 μg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC (0-24), 8.36 μg•hr/mL; range 3.2 – 47.7 μg•hr/mL. The pharmacokinetics of gemifloxacin was not

significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore Factive may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60 to 70% and is concentration independent. After repeated doses, the in vivo plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66 – 12.12 L/kg). Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours are indicated in table below.

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

Metabolism

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

Elimination

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

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%).
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.

Special Population

1) Geriatric: In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age
2) Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males. No gemifloxacin dosage adjustment based on gender is necessary.
3) Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin C_{max} was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance ≥40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance <40 mL/min
4) Hepatic Insufficiency: The pharmacokinetics following a single 320 mg dose of gemifloxacin were studied in patients with mild to severe hepatic impairments. There was a mean increase in AUC and in C_{max} in these subjects with hepatic imparement compared to healthy volunteers. These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B and C).

5.3 Preclinical safety data

1) Genotoxicity: Gemifloxacin was not mutagenic in the bacterial strains used in an Ames Salmonella reversion assay. It did not induce either micronuclei in the bone marrow of mice following intraperitoneal doses nor unscheduled DNA synthesis in hepatocytes

from rats. 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 that produced bone marrow toxicity.

2) Carcinogenesis: Long term studies in animals to determine the carcinogenic potential of gemifloxacin have not been conducted.
3) Gemifloxacin was administered orally, by gavage, 5 days per week for 12 months, to hairless mice at doses up to 100 mg/kg/day and mice were exposed to UV radiation. Gemifloxacin did not induce development of UVR-induced skin tumor. In phototoxicity studies, gemifloxacin demonstrated either the least or no phototoxic effects.
4) Gemifloxacin was reported to have antigenic potential in animal studies.
5) Impairment of Fertility: Gemifloxacin did not affect the fertility of male or female rats at AUC levels following oral administration that were approximately 3- to 4-fold higher than the AUC levels at the clinically recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone, Microcrystalline cellulose, Crospovidone, Magnesium stearate, Titanium dioxide
Hypromellose, Polyethylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Opaque PVC/PVdC/aluminium blister packs

6.6 Special precautions for disposal and other handling

Not applicable

7. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

December 27th, 2002 (Republic of Korea)

8. MANUFACTURER

LG Chem, Ltd.

151, Osongsaengmyeong 1-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea

9. DATE OF REVISION
June 2023 (ver3.0)