SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

Factive® 320 mg Film coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains: Gemifloxacin mesylate equivalent to Gemifloxacin 320 mg.

3. PHARMACEUTICAL FORM:

Film-coated tablet

White to off-white, oval, film coated tablets engraved with 'F320' on one side and break line on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indication:

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

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

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

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

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

4.2 Posology and method of administration:

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

Table 4: Recommended Dosage Regimen of FACTIVE

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

INDICATION	DOSE / DURATION
*MDRSP: multi-drug resistant *Streptococcus pneumoniae*, includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 μg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/ sulfamethoxazole.	
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily for 5 days
Community-acquired pneumonia (of mild to moderate severity)	
due to known or suspected S. pneumoniae, H. influenzae, M. pneumoniae, or C. pneumoniae infection	One 320 mg tablet daily for 5 days
due to known or suspected MDRSP, K. pneumoniae, or M. catarrhalis infection*	One 320 mg tablet daily for 7 days

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

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

Table 5. Recommended Doses for Patients with Renal Impairment

Creatinine Clearance (mL/min)	Dose
>40	See Usual Dosage
≤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.

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

Creatinine Clearance Formula

Women: 0.85 x the value calculated for men

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

Use in Elderly: No dosage adjustment is recommended.

4.3 Contraindications:

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

4.4 Special warnings and special precautions for use :

Warnings

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

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.

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.

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.

Peripheral Neuropathy: Rare 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 quinolones.

CNS Effects: In clinical studies with FACTIVE, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, FACTIVE should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in FACTIVE clinical trials, convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving other fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving FACTIVE, the drug should be discontinued and appropriate measures instituted.

***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.

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

Precautions

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

Rash: In clinical studies, rash occurred more often with FACTIVE than with 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.

Table 2. 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.

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.

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.

4.5 Interaction with other medications and another forms of interaction:

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

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

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

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 Cmax of 19% and 12%. These changes are not considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 μg/150 μg once daily for 21 days to healthy female subjects).

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

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

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

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

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.

Geriatric Use: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as FACTIVE. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, 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.

4.6 Pregnancy and lactation:

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

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

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

4.7 Effects on ability to drive and use machines:

Not applicable.

4.8 Undesirable effects:

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 gemifloxacin in clinical pharmacology studies. The majority of adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity.

FACTIVE was discontinued because of an adverse event (determined by the investigator to be possibly or probably related to drug) in 2.0% of patients, primarily due to rash (0.8%), nausea (0.3%), diarrhea (0.3%), urticaria (0.2%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an adverse event at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.4%), vomiting (0.3%), rash (0.3%), abdominal pain (0.2%) and vertigo (0.2%).

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

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Factive® 320mg Film Coated Tablets

Gemifloxacin 320 Tablets

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Adverse Events with a Frequency of Less than 1%

Additional drug-related adverse events (possibly or probably related) in the 8119 patients, with a frequency of >0.1% to ≤1% included: abdominal pain, anorexia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, genital pruritus, hyperglycemia, increased alkaline phosphatase, increased ALT, increased AST, increased creatine phosphokinase, insomnia, leukopenia, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

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

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

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

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

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

4.9 Overdose

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

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

5. PHARMACEUTICAL PROPERTIES:

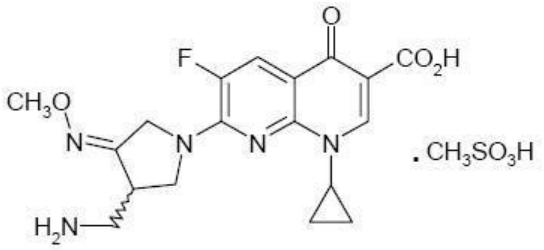
Pharmacotherapeutic Group:

5.1 Pharmacodynamic properties

ATC code: J01MA15

FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 µg/mL at 37ºC, pH 7.0). Its empirical formula is C18H20FN5O4•CH4O3S and its chemical structure is:



Gemifloxacin Mesylate

Factive® Film Coated Tablets

Gemifloxacin 320 mg Tablets

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 (Cmax) and systemic drug exposure (AUC (0-24)) were 1.61 ± 0.51 μg/mL (range 0.70-2.62 μg/mL) and 9.93 ± 3.07 μg•hr/mL (range 4.71-20.1 μg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC (0-24), 8.36 μg•hr/mL; range 3.2 – 47.7 μg•hr/mL).

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

Distribution

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

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

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

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

Metabolism

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

Excretion

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

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Povidone
Microcrystalline Cellulose
Crospovidone
Magnesium Stearate
Opadry

Factive® 320mg Film Coated Tablets

Gemifloxacin 320 Tablets

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

3 years.

6.4 Special precautions for storage:

Store below (30 °C).

Do not use beyond the Imprinted expiry data or if the product shows any visible signs of deterioration.

6.5 Nature and content of the container.

Aluminum- PVC/PVDC blister, packed in a printed carton with folded leaflet.

Primary packaging:

Aluminum – PVC-PVDC.

Secondary packaging:

Carton: A carton with an over printed information.

Leaflet*:* multi folded leaflet

Pack details:

One Aluminum- PVC/PVDC blister of 5 tablets each, packed in a printed carton with folded leaflet.

One Aluminum- PVC/PVDC blister of 7 tablets each, packed in a printed carton with folded leaflet.

Pack size:

Packs of 5 Tablets.

Packs of 7 Tablets.

Hospital packs are available.

Factive® 320mg Film Coated Tablets

Gemifloxacin 320 Tablets

6.6 Instruction for use and handling:

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.

- Strictly follow the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are experts in medicine, its benefits and risks.

- Do not by yourself interrupt the period of treatment prescribed for you.

- Do not repeat the same prescription without consulting your doctor.

- Keep medicament out of reach of children.

7. MARKETING AUTHORIZATION HOLDER

Tabuk Pharmaceutical Manufacturing Company

P.O. Box 3633

Tabuk - Saudi Arabia

Tel: 009661-4-4283030

Fax: 009661-4-4283031/421-0286

8. MARKETING AUTHORISATION NUMBER(S)

- Marketing Authorization Numbers in Ethiopia: 05348/07309/REN/2020

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

- Date of first authorization in Ethiopia: 29 September 2011

- Date of latest renewal in Ethiopia: 24 September 2020

10. DATE OF REVISION OF THE TEXT

August 2023