1. NAME OF THE MEDICINAL PRODUCT
Safgem Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains: Gemifloxacin as Mesylate 320mg

3. PHARMACEUTICAL FORM
Film-coated tablet
White to almost white, oblonged, biconvex coated tablet with break line on one side, S engraved on left and F on right side of line.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
SAFGEM is indicated for the treatment of the following bacterial infections in adults caused by sensitive organisms as follows:

Respiratory Tract Infections:

- Community acquired pneumonia (CAP) caused by *S. pneumoniae, C. pneumoniae, M. pneumoniae, H. influenzae, M. catarrhalis, L. pneumophila*
- Acute exacerbations of chronic bronchitis (AECB**)** caused by *H. influenzae, M. catarrhalis, S. pneumoniae*
- Acute bacterial sinusitis caused by *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus*

Urinary Tract Infections:

- Acute uncomplicated pyelonephritis caused by *E. coli, K. pneumoniae*
- Uncomplicated urinary tract infections (uUTI) in females caused by *E. coli, K. pneumoniae*

4.2 Posology and method of administration
Posology

Safgem can be taken with or without food and should be swallowed with a liberal amount of liquid. The recommended dose of **Safgem** is 320 mg daily, according to the following table:

INDICATION	DOSE	DURATION
Acute bacterial exacerbations of chronic bronchitis	One 320 mg tablet daily	5 days
Acute sinusitis	One 320 mg tablet daily	5 days
Community-acquired pneumonia	One 320 mg tablet daily	7 days*
Uncomplicated urinary tract infections	One 320 mg tablet daily	3 days
Acute pyelonephritis	One 320 mg tablet daily	10 days

* Therapy may be extended to 14 days of therapy in cases of serious pneumonia.

Renally Impaired Patients: Dose adjustment in patients with mild/moderate renal impairment is not required. Some modification of dosage is recommended for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment:

Creatinine Clearance (mL/min)	Dose
≥40	See Usual Dosage
<40	160 mg q24h

Patients on haemodialysis or continuous ambulatory peritoneal dialysis therapy should receive 160 mg q24h.

Hepatic impairment: SAFGEM may be given to patients with hepatic impairment, with no requirement for dose adjustment.

Elderly patients: Dose adjustment is not required.

Method of administration

Safgem Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

SAFGEM 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 precautions for use

***Tendinopathy and Tendon Rupture*:** Fluoroquinolones, including SAFGEM, 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. SAFGEM 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.

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

QT Effects: Fluoroquinolones may prolong the QT interval in some patients. SAFGEM 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. SAFGEM 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 SAFGEM treatment in over 8119 patients, including 707 patients concurrently receiving drugs known to prolong the QTc interval and 7 patients with hypokalemia.

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

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

SAFGEM 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 SAFGEM. 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.

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 SAFGEM, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, SAFGEM should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in SAFGEM clinical trials, convulsions, increased intracranial pressure, 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 SAFGEM, 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 SAFGEM, 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.

PRECAUTIONS

General: Prescribing SAFGEM 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 SAFGEM 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 SAFGEM patients than in comparator patients (0.6% vs. 0.2%). SAFGEM should be discontinued in patients developing a rash or urticaria while on treatment.

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

Gender & Age (yr) Category	Duration of SAFGEM 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 SAFGEM 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 SAFGEM 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 SAFGEM 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 SAFGEM should be maintained to prevent the formation of a highly concentrated urine.

4.5 Interaction with other medicinal products and other 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 SAFGEM 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 SAFGEM 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%.

4.6 Fertility, pregnancy and lactation

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 SAFGEM in pregnant women has not been established. SAFGEM 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, SAFGEM should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

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

Geriatric Use: Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as gemifloxacin 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 SAFGEM to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue SAFGEM and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur Of the total number of subjects in clinical studies of SAFGEM, 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 event rate for this group was similar to or lowers 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.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, SAFGEM 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).

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that Gemifloxacin may have an effect: on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

In clinical studies, 8119 patients received daily oral doses of 320 mg SAFGEM. 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.

SAFGEM 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 SAFGEM versus comparator drug (beta-lactam antibiotics, macrolides or other fluoroquinolones) are as follows: diarrhea 5.0% vs. 6.2%; rash 3.5% vs. 1.1%; nausea 3.7% vs. 4.5%; headache 4.2% vs. 5.2%; abdominal pain 2.2% vs. 2.2%; vomiting 1.6% vs. 2.0%; and dizziness 1.7% vs. 2.6%.

Adverse Events with a Frequency of Less than 1%

Additional drug-related adverse events (possibly or probably related) in the 8119 patients, 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 SAFGEM

	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, < 40 years	NA*		1/37	2.7	8/88	9.1
Females, ≥ 40 years	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
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

Laboratory Changes: The percentages of patients who received multiple doses of SAFGEM and had a laboratory abnormality are listed below. It is not known whether these abnormalities were related to SAFGEM 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 SAFGEM 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 SAFGEM treated patients had elevated ALT values immediately prior to entry into the study. Of these patients, 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 gemifloxacin or 250 mg BID of ciprofloxacin for 3 days, there was an increased incidence of ALT elevations in the gemifloxacin arm (3.9%) vs. the comparator arm (1.0%). In this study, two patients experienced ALT

elevations of 8 to 10 times the upper limit of normal. These elevations were asymptomatic and reversible.

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

The following are additional adverse reactions reported during the post-marketing use of SAFGEM. 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 SAFGEM exposure:

- anaphylactic reaction, erythema multiforme, skin exfoliation, facial swelling;
- 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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
No specific antidote is known. Dialysis does not remove gemifloxacin sufficiently to be useful in 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, treated symptomatically and adequate hydration should be maintained.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties
Pharmacotherapeutic group: Fluoroquinolones
ATC code: J01MA15

5.2 Pharmacokinetic properties
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

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 SAFGEM 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.

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).

Pharmacokinetics in special populations

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

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

Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 µg•hr/mL (range, 3.21 – 42.71 µg•hr/mL) and 8.80 µg•hr/mL (range, 3.33 – 47.73 µg•hr/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

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

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

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic

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

Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin Cmax was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 creatinine clearance ≤40 mL/min. Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg BID, or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Starch
- Avicel 102
- Aerosil 200
- Lactose
- Primogel
- Magnesium Stearate
- Isopropyl Alcohol
- Opadry white
- PEG 6000
- Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C
Protect from light.

6.5 Nature and contents of container
Aluminium/Aluminium blister

Pack sizes: 1x07's film-coated tablets

6.6 Special precautions for disposal and other handling
No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Dispensing Requirements:
Safgem 320mg Tablet is dispensed only on the prescription of registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER
Saffron Pharmaceuticals Pvt. Ltd.
19 km, Sheikhupura Road Faisalabad Pakistan.