1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Summary of Product Characteristics

1.3.1.1 Invented Name of the Medicinal Product

GSPAR 200

Sparfloxacin Tablets 200 mg

1.3.1.2 Strength

Sparfloxacin 200 mg

1.3.1.3 Dosage Form

Solid Dosage Form

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:

Sparfloxacin……..200 mg

Excipients…….....Q.S.

Colour: Approved colour used

For a full list of excipients see section 1.3.1.8.1

1.3.1.5 PHARMACEUTICAL FORM

Film Coated Tablets

Yellow coloured, elongated, biconvex, Film· coated tablets, with breakline on one side and other side is plain.

1.3.1.6. CLINICAL PARTICULARS

1.3.1.6.1 Therapeutic indications

Sparfloxacin is indicated for the treatment of adults (≥ 18 years of age) with the following infections caused by susceptible strains of the designated microorganisms:

Community-acquired pneumonia caused by Chlamydia pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, or Streptococcus pneumoniae Acute bacterial exacerbations of chronic bronchitis caused by Chlamydia pneumoniae, Enterobacter cloacae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiellapneumoniae, Moraxella catarrhalis, Staphylococcus aureus, or Streptococcus pneumonia Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to sparfloxacin.

Therapy with sparfloxacin may be initiated before results of these tests are known;

Once results become available, appropriate therapy should be selected. Culture and susceptibility testing performed periodically during therapy will provide information on the continued susceptibility of the pathogen to the antimicrobial agent and also on the possible emergence of bacterial resistance.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology and Method of administration

Sparfloxacin can be taken with or without food.

Antacids containing magnesium and aluminum or sucralfate or (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may be taken 4 hours after administration of sparfloxacin.

The recommended daily dose of sparfloxacin in patients with normal renal function is two 200-mg tablets taken on the first day as a loading dose. Thereafter, one 200-mg tablet should be taken every 24 hours for a total of 10 days of therapy (11 tablets). The recommended daily dose of sparfloxacin in patients with renal impairment (creatinine clearance < 50 mL/min) is two 200-mg tablets taken on the first day as a loading dose. Thereafter, one 200-mg tablet should be taken every 48 hours for a total of 9 days of therapy (6 tablets).

1.3.1.6.3 CONTRAINDICATIONS

Sparfloxacin is contraindicated for individuals with a history of hypersensitivity or Photosensitivity reactions.

1.3.1.6.4 WARNING AND PRECAUTIONS

MODERATE TO SEVERE PHOTOTOXIC REACTIONS HAVE OCCURRED IN PATIENTS EXPOSED TO DIRECT OR INDIRECT SUNLIGHT OR TO ARTIFICIAL ULTRAVIOLET LIGHT (e.g., SUNLAMPS) DURING OR FOLLOWING TREATMENT. THESE REACTIONS HAVE ALSO OCCURRED IN PATIENTS EXPOSED TO SHADED OR DIFFUSE LIGHT, INCLUDING EXPOSURE THROUGH GLASS OR DURING CLOUDY WEATHER. PATIENTS SHOULD BE ADVISED TO DISCONTINUE SPARFLOXACIN THERAPY AT THE FIRST SIGNS OR SYMPTOMS OF A PHOTOTOXICITY REACTION SUCH AS A SENSATION OF SKIN BURNING, REDNESS, SWELLING, BLISTERS, RASH, ITCHING, OR DERMATITIS.

The overall incidence of drug related phototoxicity in the 1585 patients who received sparfloxacin during clinical trials with recommended dosage was 7.9% (n=126). Phototoxicity ranged from mild 4.1% (n=65) to moderate 3.3% (n=52) to severe 0.6% (n=9), with severe defined as involving at least significant curtailment of normal daily activity. The frequency of phototoxicity reactions characterized by blister formation was 0.8% (n=13) of which 3 were severe. The discontinuation rate due to phototoxicity independent of drug relationship was 1.1% (n=17).

As with some other types of phototoxicity, there is the potential for exacerbation of the reaction on re-exposure to sunlight or artificial ultraviolet light prior to complete recovery from the reaction. In a few cases, recovery from phototoxicity reactions was prolonged for several weeks. In rare cases, reactions have recurred up to several weeks after stopping sparfloxacin therapy.

EXPOSURE TO DIRECT AND INDIRECT SUNLIGHT (EVEN WHEN USING SUNSCREENS OR SUNBLOCKS) SHOULD BE AVOIDED WHILE TAKING SPARFLOXACIN AND FOR FIVE DAYS FOLLOWING THERAPY. SPARFLOXACIN THERAPY SHOULD BE DISCONTINUED IMMEDIATELY AT THE FIRST SIGNS OR SYMPTOMS OF PHOTOTOXICITY.

These phototoxic reactions have occurred with and without the use of sunscreens or sunblocks and have been associated with a single dose of sparfloxacin. However, a study in healthy volunteers has demonstrated that some sunscreen products, specifically those active in blocking UVA spectrum wavelengths (those containing the active ingredients octocrylene or Parsol® 1789), can moderate the photosensitizing effect of sparfloxacin. However, many over-the-counter sunscreens do not provide adequate UVA protection.

Increases in the QTc interval have been observed in healthy volunteers treated with sparfloxacin. After a single loading dose of 400 mg, a mean increase in QTc interval of 11 msec (2.9%) is seen; at steady-state the mean increase is 7 msec (1.9%). The magnitude of the QTceffect does not increase with repeated administration, and the QTc returns to baseline within 48 hours of the last dose. In clinical trials involving 1489 patients with a baseline QTcmeasurement, the mean prolongation at steady-state was 10 msec (2.5%); 0.7% of patients had a QTc interval greater than 500 msec; however, no arrhythmic effects were seen.

In a covariate analysis, age did not have a statistically significant contribution to the change in QTc recorded in patients taking sparfloxacin. However, in controlled clinical trials, QTc interval prolongation was more frequently reported as an adverse event in patients $\geq$ 65 years of age than in younger patients. In these clinical trials, QTc interval prolongation was reported more frequently as an adverse event (defined as QTc $\geq$ 0.440 sec or $\geq$ 15% change from baseline) in elderly patients treated with sparfloxacin than in elderly patients treated with a comparator drug. During post marketing surveillance, cardiovascular events including torsades de pointes and other arrhythmias were more frequent in the elderly than in younger patients treated with sparfloxacin although a history of underlying cardiac disease in this population was more common. Sparfloxacin is contraindicated in patients with known QTc prolongation.

CARCINOGENESIS

Sparfloxacin was not carcinogenic in mice or rats when administered for 104 weeks at daily oral doses 3.5 - 6.2 times greater than the maximum human dose (400 mg), respectively, based upon mg/m². These doses corresponded to plasma concentrations approximately equal to (mice) and 2.2 times greater than (rats) maximum human plasma concentrations.

In a study of repeated exposure (5 days per week for 40 weeks) of hairless albino mice (SKH-1) to a low dose (0.272 Caucasian human minimal erythema dose [MED]) of solar simulated UV radiation, skin tumors were induced with a median onset time of 43 weeks. As expected for this model, the gross appearance of the tumors in this study was consistent with squamous cell carcinoma or its precursors. When sparfloxacin (6.0 or 12.5 mg/kg/day) was administered by the oral route, the

median tumor onset time was reduced to 38 and 32 weeks, respectively. This reduction in median onset time was similar to that observed when mice were exposed to a higher dose (0.476 Caucasian human MED) of solar simulated UV radiation alone. At a dose level of 12.5 mg/kg/day, mice had skin sparfloxacin concentrations (± SD) of approximately 1.8 µg/g (± 0.26, N=6). Following a 400 mg dose of sparfloxacin, skin levels measured in human subjects averaged 5.5 µg/g (± 6.5, N=11). A similar effect on the time to the development of skin tumors has been observed in this mouse strain with some other fluoroquinolone antibiotics. The clinical significance of these findings to humans is unknown.

MUTAGENESIS

Sparfloxacin was not mutagenic in Salmonella typhimurium TA98, TA100, TA1535, or TA1537, in Escherichia coli strain WP2 uvrA, nor in Chinese hamster lung cells. Sparfloxacin and other quinolones have been shown to be mutagenic in Salmonella typhimurium strain TA102 and to induce DNA repair in Escherichia coli, perhaps due to their inhibitory effect on bacterial DNA gyrase. Sparfloxacin induced chromosomal aberrations in Chinese hamster lung cells in vitro at cytotoxic concentrations; however, no increase in chromosomal aberrations or micronuclei in bone marrow cells was observed after sparfloxacin was administered orally to mice.

When Chinese hamster ovary cells were incubated with sparfloxacin in the presence of solar simulated UV radiation, chromosome aberrations were induced at concentrations of sparfloxacin that were not associated with aberrations in the absence of UV.

The low level of UV used in the experiment, approximately 375 mJ/cm², was not, by itself, associated with chromosome aberrations, while the high level of UV used in the experiment, approximately 750 mJ/cm², induced fewer aberrations than sparfloxacin plus low or high dose UV.

IMPAIRMENT OF FERTILITY

Sparfloxacin had no effect on the fertility or reproductive performance of male or female rats at oral doses up to 15.4 times the maximum human dose (400 mg) based upon mg/m² (equivalent to approximately 12 times the maximum human plasma concentration)

1.3.1.6.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Digoxin

Sparfloxacin has no effect on the pharmacokinetics of digoxin.

Methylxanthines

Sparfloxacin does not increase plasma theophylline concentrations. Since there is no interaction with theophylline, interaction with other methylxanthines such as caffeine is unlikely.

Warfarin

Sparfloxacin does not increase the anti-coagulant effect of warfarin.

Cimetidine

Cimetidine does not affect the pharmacokinetics of sparfloxacin.

Antacids and Sucralfate

Aluminum and magnesium cations in antacids and sucralfate form chelation complexes with sparfloxacin. The oral bioavailability of sparfloxacin is reduced when an aluminum-magnesium suspension is administered between 2 hours before and 2 hours after sparfloxacin administration. Similarly, the oral bioavailability of sparfloxacin may be reduced when; (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution is administered between 2 hours before and 2 hours after sparfloxacin administration. The oral bioavailability of sparfloxacin is not reduced when the aluminum-magnesium suspension is administered 4 hours following sparfloxacin administration.

Zinc/iron salts

Absorption of quinolones is reduced significantly by these preparations. These products may be taken 4 hours after sparfloxacin administration.

Probenecid

Probenecid does not alter the pharmacokinetics of sparfloxacin.

1.3.1.6.6 PREGNANCY AND LACTATION

Pregnancy

Sparfloxacin has been assigned to pregnancy category C by the FDA. High-dose animal studies revealed no evidence of teratogenicity. However, when studied in rats at maternally toxic doses (9.3 times the maximum human dose based on mg/m2) there was an increased incidence of fetuses with ventricular septal defects. This event was not observed in monkeys or rabbits at maternally toxic doses. There are no controlled data in human pregnancy. Surveillance studies have not reported an increased risk of major birth defects. However, cartilage damage and arthropathies are reported in immature animals exposed to quinolones, giving rise to concern over effects on fetal bone formation. Because safer alternatives are available, some experts consider sparfloxacin contraindicated during pregnancy, especially during the first trimester.

The manufacturer only recommends use of sparfloxacin during pregnancy when benefit outweighs risk of 549 cases reported by the European Network of Teratology Information Services involving exposure to other fluoroquinolones, congenital malformations were reported in 4.8%; however, this was not higher than the background rate.

Breast-feeding

Sparfloxacin is excreted into human milk. Cartilage erosion and arthropathy have been reported in immature animals giving rise to concern over toxic effects in the developing joints of nursing infants. The manufacturer recommends that due to the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

1.3.1.6.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about the potential for central nervous system effects, and advised not to drive or operate machinery whilst taking sparfloxacin.

1.3.1.6.8 UNDESIRABLE EFFECTS

Photo toxicity including manifestations of sunburn, erythema and severe bullous lesions. Recurrence of the symptoms after a new sun exposure, several weeks after the end of the treatment, has been sometimes observed.

Skin reactions: rash, pruritus, swelling, blisters.

Musculoskeletal: muscle or joint pain, tendinitis, ruptured tendon.

Cardiovascular: rare cardiac rhythm disorders including torsades de pointes, arrhythmia, bradycardia, tachycardia and ventricular tachycardia.

Digestive disorders: nausea, vomiting, diarrhoea, abdominal pain, gastralgia.

Nervous System: tremor, feeling drunk, paraesthesia, sensory disturbance, headache and vertigo.

Psychiatric disorders: hallucinations, sleep disorders at the beginning of treatment.

Body as a whole: rare cases of hypersensitivity, including urticaria, angioedema, anaphylactic shock and Quincke's oedema.

Hematologic System: isolated cases of thrombocytopenia and rare cases of thrombocytopenic purpura.

1.3.1.6.9 OVERDOSE

In case of overdose, the patient should be monitored in a suitably equipped unit and advised to avoid sun exposure for 5 days. ECG monitoring is recommended due to the possible prolongation of the QTc interval. There is no known antidote for sparfloxacin over dosage.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

1.3.1.7.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotic from the Quinolone class.

Sparfloxacin, an aminodifluoroquinolone, is a synthetic antibiotic belonging to the quinolone family. Sparfloxacin exhibits a spectrum of activity which is related to the therapeutic indication and focused on S.pneumoniae. However, other bacterial species usually susceptible to sparfloxacin can be associated in community acquired pneumonia. In such a situation, no combination therapy is needed because of a spectrum of activity which includes all respiratory pathogens.

- Susceptible species (MIC _ 1 mg/l):

Streptococcus pneumoniae including those strains resistant to beta-lactam and macrolide antibiotics

Streptococcus of groups A, C and G

Methicillin-susceptible *Staphylococcus*

Haemophilus influenzae including beta-lactamase producing strains

Moraxella catarrhalis

Mycoplasma pneumoniae, Chlamydia psittaci and pneumoniae Legionella

- Resistant species (MIC > 2 mg/l):

Methicillin-resistant *Staphylococcus*

1.3.1.7.2 Pharmacokinetic properties

Absorption

The absorption of sparfloxacin is rapid with peak serum concentrations achieved 3 to 5 hours after the first dose. Oral absorption is not modified by the presence of food. Steady-state plasma concentrations are achieved on the first day due to the loading dose that is double the daily dose.

Dosing regimen	Day 1		Steady state	
	Cmax µg/ml	Cmin µg/ml	Cmax µg/ml	Cmin µg/ml
400 mg*/ 200 mg**	1.7	0.6	1.4	0.5

* Loading dose, ** Daily dose.

Distribution

After a loading dose of 400 mg, the concentrations found in the extravascular fluid are equivalent to plasma concentrations. In bronchopulmonary tissues, concentrations reached are greater than the MIC of the bacterial species susceptible to sparfloxacin: 10 µg/g in pulmonary parenchyma, 16.7 µg/ml in alveolar surfactant and 2-5 µg/g in bronchial mucosa.

Sparfloxacin concentrates preferentially in macrophages, in which concentrations of 40-50 µg/g are reached. Plasma protein binding is 45 %.

Metabolism

Sparfloxacin is metabolized in the liver to an inactive glucuronide conjugate. Metabolism does not depend on cytochrome mediated oxidation, in particular the cytochrome P450 system.

Elimination

The terminal plasma elimination half-life is approximately 20 hours. Excretion is both fecal and urinary: two-thirds is excreted in the feces as unchanged sparfloxacin, one-third is eliminated in the urine as unchanged sparfloxacin and as the glucuronide conjugate. Biliary excretion, mainly as the glucuronide conjugate, accounts for 10-20 % of the administered dose.

1.3.1.7.3 Preclinical safety data

Sparfloxacin exhibits the toxicity profile as following:

- Hepatotoxicity based on an increase in hepatic enzymes (e.g. aspartaminotransferase) and a cytologic alteration of the hepatocytes, notably vacuolisation and multifocal or single cell liver necrosis;

- Nephrotoxicity, notably glomerulo-nephritis and interstitial nephritis;

- Cardiotoxicity with a pronounced prolongation of the QT interval, occured already in doses close to human dosage;

- Arthrotoxicity;

- Phototoxicity;

Under simultaneous U.V. exposure, sparfloxacin can exhibit mutagenic properties and carcinogenetic effects. Reproductive toxicity studies detected anomalies such as ventricular septum defect in young rats, but these effects were not observed in young monkeys.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Maize Starch
Microcrystalline Cellulose
Lactose
Maize Starch
Purified Water
Magnesium Stearate
Talcum Powder
Sodium Starch Glycolate
Fumed Silica
Hydroxypropyl methyl cellulose
Titanium Dioxide
Polyethylene Glycol 4000
Talcum Powder
Isopropyl Alcohol
Methylene Chloride
Lake Quinoline Yellow

1.3.1.8.2 Incompatibilities: Not applicable.

1.3.1.8.3 Shelf life: Three years.

1.3.1.8.4 Special precautions for storage: Store below 30°C. Protected from light.

1.3.1.8.5 Nature and contents of container

Available as Alu-Alu blister pack of 07tablets. Such 01 blister packed in a carton along with pack insert.

1.3.1.8.6 Special precautions for disposal and other Special handling

None

1.3.1.9 Marketed by:

M/S. GREENLIFE PHARMACEUTICALS LTD.,
35A, ASSOCIATION AVENUE, ILUPEJU, LAGOS,
NIGERIA.,

1.3.1.10 Manufactured by:

M/s. McW Healthcare (P) Ltd.
286, 287A, 287B,
Sector-E, Industrial Area,
Sanwer Road,
Indore (M.P.) India