1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals

1. NAME OF THE MEDICINAL PRODUCT

1.1 Invented Name of the Medicinal Product

GFLOX 400

Ofloxacin Extended Release Tablets 400 mg

1.2 Strength

Ofloxacin USP 400 mg

1.3 Pharmaceutical Form

Solid oral dosage form

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Extended Release Film Coated Tablet Contains:

Ofloxacin USP…… 400 mg

Excipients ……... .q.s.

Colour: Titanium Dioxide BP

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Solid Oral Dosage Form

White capsule shaped, biconvex, film coated tablet with a break line on one side other side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GFLOX 400 is indicated for following:

- Lower respiratory tract infections including pneumonia caused by H. influenza and Streptococcus pneumoniae and acute exacerbation of chronic bronchitis;
- Upper and lower urinary tract infections;
- Acute, uncomplicated urethral and cervical gonorrhoea;
- Nongonococcal urethritis and cervicitis due to Chlamydia trachomatis and Neisseria gonorrhoeae;
- Uncomplicated skin and soft-tissue infections;
- Acute pelvic inflammatory disease (including severe infection);
- Prostatitis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The tablets must be taken after meals and swallowed whole.

Usual adult dose:

Impaired hepatic function:

In patients with severely impaired liver function as in cases of cirrhosis of the liver with ascites, ofloxacin elimination may be reduced.

A maximum dose of 400 mg of ofloxacin per day should therefore not be exceeded.

4.3 CONTRAINDICATIONS

History of hyper-sensitivity to ofloxacin or members of the quinolone group of antimicrobial agents.

4.4 WARNING AND PRECAUTIONS

General:

Photo-toxicity has been observed in some patients receiving fluoroquinolones. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs. Ofloxacin should be used with caution in patients with epilepsy or a history of CNS disorders.

Warnings:

The safety and effectiveness of ofloxacin in paediatric patients, adolescents (less than 18 years of age), pregnant women, and lactating women have not been established. Patients hypersensitive to one fluoroquinolone or other chemically related quinolone derivatives may be hypersensitive to ofloxacin as well.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Geriatrics:

No geriatrics-specific problems have been documented till date that could limit the usefulness of fluoroquinolones in the elderly. However, elderly patients are more likely to have an age related decrease in renal function, which may require an adjustment of dosage in patients receiving fluoroquinolones.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Theophylline:

Ofloxacin is not thought to cause a pharmacokinetic interaction with theophylline, unlike some other fluoroquinolones.

Antacids, sucralfate, metal cations, multivitamins:

Absorption of quinolones is decreased with these agents, therefore concurrent administration of ofloxacin should be avoided.

Probenecid:

Urinary excretion of certain other quinolones is reduced by the concomitant administration of probenecid.

NSAIDs:

Concurrent use of NSAIDs has been reported to increase the CNS effects of quinolones.

Cyclosporine:

Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine use of cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.

Drugs metabolized by Cytochrome P450 enzymes:

Most quinolone antimicrobial drugs inhibit cytochrome P450 enzyme activity. This may result in a prolonged half-life for some drugs that are also metabolized by this system (e.g. cyclosporine, theophylline, warfarin, etc.) when co-administered with quinolones. The extent of this inhibition varies among different quinolones.

Warfarin:

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Cimetidine:

Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in half-life and AUC of some quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.

Antidiabetic agents:

Since disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended when these agents are used concomitantly.

Laboratory value alterations:

Serum alkaline phosphatase, SGOT, SGPT and lactate dehydrogenase: Values may be increased during ofloxacin treatment.

Urinary opiates and porphyrins: False positive results may occur.

4.6 PREGNANCY AND LACTATION

Pregnancy:

There are no adequate and well-controlled studies in pregnant women. Ofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation:

Ofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug in the mother.

Paediatrics:

Fluoroquinolones are not recommended for use in children and adolescents (under the age of 18 years).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since there have been occasional reports of drowsiness/somnolence, impairment of skills, dizziness/vertigo and visual disturbances, which may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery), patients should know how they react to ofloxacin before they drive or operate machinery. These effects may be enhanced by alcohol.

4.8 UNDESIRABLE EFFECTS

The overall frequency of adverse reactions from the clinical trial database is about 7%. The commonest events involved the gastro-intestinal system (about 5.0%) and the nervous system (about 2.0%). The following provides a tabulation based on post marketing experience with ofloxacin where occasional represents a frequency of 0.1 - 1.0%, rare <0.1%, very rare <0.01% and isolated cases <0.01%.

Digestive and liver side effects:

Occasional: Nausea and vomiting, diarrhoea, abdominal pain, gastric symptoms (diarrhoea may sometimes be a symptom of enterocolitis which may, in some cases, be haemorrhagic).

Rarely, Loss of appetite, increase in liver enzymes and/or bilirubin.

Very rare- cholestatic jaundice, hepatic or severe liver damage may develop.

A particular form of enterocolitis that can occur with antibiotics is pseudomembranous colitis (in most cases due to Clostridium difficile). Even if Clostridium difficile is only suspected, administration of ofloxacin should be discontinued immediately and appropriate treatment given. Drugs that inhibit peristalsis should not be administered in such cases.

CNS:

Occasional- Headache, dizziness, sleep disorders, restlessness.

Rarely, Confusion, nightmares, anxiety, depression, hallucinations and psychotic reactions, drowsiness, unsteady gait and tremor (due to disorders of muscular co-ordination), neuropathy, numbness and paraesthesiae or hyperaesthesiae, visual disturbances, disturbances of taste and smell (including, in exceptional cases, loss of function) extrapyramidal symptoms.

Very rarely, Convulsions, hearing disorders (including, in exceptional cases, loss of hearing). These reactions have occurred in some patients after the first dose of ofloxacin, in such cases, discontinue treatment immediately.

Cardiovascular system:

Tachycardia and a temporary decrease in blood pressure have been reported.

Rarely, Circulatory collapse (due to pronounced drop in blood pressure).

Haematological side effects:

Very rare- anaemia, leucopenia (including agranulo-cytosis), thrombocytopenia, pancytopenia. Only in some cases are these due to bone marrow depression. In very rare cases, haemolytic anaemias may develop.

Renal side effects:

Rarely, Disturbances of kidney function.

Isolated cases- Acute interstitial nephritis, or an increase in serum creatinine, which may progress to acute renal failure.

Allergic and skin side effects:

Occasional- Skin rash, itching**.**

Very rarely, Rash on exposure to strong sunlight, other severe skin reactions, hypersensitivity reactions, immediate or delayed, usually involving the skin (e.g. erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, and vasculitis) may occur. In exceptional circumstances, vasculitis can lead to skin lesions including necrosis and may also involve internal organs.

There are rarely other signs of anaphylaxis such as tachycardia, fever, dyspnoea, shock, angioneurotic oedema, vasculitic reactions, eosinophilia. In such cases, treatment should be discontinued immediately and where appropriate, supportive treatment given.

Isolated cases- Pneumonitis.

Other side effects: Rare- Malaise.

Very rarely, Excessive rise or fall in blood sugar levels, weakness, joint and muscle pains (in isolated cases these may be symptoms of rhabdomyolysis).

Isolated cases- Tendon discomfort including inflammation and rupture of tendons (e.g. the Achilles tendon) particularly in patients treated concurrently with corticosteroids. In the event of signs of inflammation of a tendon, treatment with ofloxacin must be stopped immediately and appropriate treatment must be initiated for the affected tendon.

The possibility cannot be ruled out that ofloxacin may trigger an attack of porphyria in predisposed patients. Except in very rare instances (e.g. isolated cases of smell, taste and hearing disorders) the adverse effects observed subsided after discontinuation of ofloxacin.

4.9 OVERDOSE

As there is no specific antidote for ofloxacin, overdose treatment should be symptomatic and supportive and may include the following:

- Induction of emesis or use of gastric lavage to empty the stomach;
- Maintenance of adequate hydration;
- Supportive Therapy.

Ofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone Antibacterials, Fluoroquinolones

ATC code: J01 MA 01

Mechanism of action

Ofloxacin inhibits bacterial DNA replication by inhibiting bacterial topoisomerases, particularly DNA gyrase and topoisomerase IV. It is active after oral administration.

Therapeutic doses of ofloxacin are devoid of pharmacological effects on the voluntary or autonomic nervous system.

The NCCLS MIC breakpoint recommendations are as follows:

S ≤ 2 mg/l and R ≥ 1 mg/l

Haemophilus influenzae and Neisseria gonorrhoea are exceptions with breakpoints at S ≤ 0.25 mg/l and R ≥ 1 mg/l

The BSAC general recommendations are S ≤ 2 mg/l and R ≥ 4 mg/l

According to DIN 58 940, the following limits apply for ofloxacin:

S ≤ 1 mg/L, I = 2 mg/L, R ≥ 4 mg/L.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ofloxacin or not.

Only those pathogens relevant to the indications are listed.

	European range of acquired bacterial resistance to ofloxacin
Normally susceptible	
Aerobic Gram-positive micro organisms	
S. aureus - methicillin-sensitive	0.3-12.6%
S. pyogenes	2-5%
Aerobic Gram-negative micro organisms	
Acinetobacter spp	0.3-7.3%
Citrobacter spp.	3-15%
Enterobacter spp.	2-13%

E. coli	1-8%
H. influenzae	1%
Klebsiella spp.	1-10%
Moraxella spp.	0-0.2%
Morganella morganii	0-6.9%
N. gonorrhoeae	25%
Proteus spp.	1-15%
Serratia marcescens	2-2.4%
Others	
Chlamydia spp	
L. pneumophila	
Intermediately susceptible	
Aerobic Gram-positive micro organisms	
S. pneumoniae	70%
Providentia	17.1%
Aerobic Gram-negative micro organisms	
E. faecalis	50%
P. aeruginosa	20-30%
Serratia spp.	20-40%
Stenotrophomonas maltophilia	5.1-11%
Others	
Mycoplasma spp.	0-5.3%
Ureaplasma spp.	0-2.1%
Resistant	
Anaerobic bacteria	
S. aureus - methicillin-resistant	69.2-85.7%
T. pallidum	

Resistance

The main mechanism of bacterial resistance to ofloxacin involves one or more mutations in the target enzymes, which generally confer resistance to other active substances in the class. Efflux

pump and impermeability mechanisms of resistance have also been described and may confer variable resistance to active substances in other classes.

5.2 Pharmacokinetic properties:

Ofloxacin is well absorbed when given orally.

Following single dose administration, peak plasma concentrations of about 1.09 + 0.46 mcg/mL is obtained 6-8 hours after administration of ofloxacin 400 mg tablets. The AUC0-t values obtained ise 21.98 + 4.59 mcg.h/mL.

The administration of ofloxacin with food does not affect the Cmax and AUC of the drug, but Tmax is prolonged. The plasma protein binding of ofloxacin is about 31% and the plasma elimination half-life is about 6-8 hours. Ofloxacin is widely distributed in the tissues and body fluids viz. lung, skin, blister fluid, cervix ovary, prostatic fluid, prostatic tissue and sputum.

Ofloxacin is eliminated mainly by the kidneys. About 65-80% of an oral dose is excreted unchanged in the urine and less than 5% as metabolites viz. desmethyl or N-oxide metabolite. Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearance <50 mL/min), and dosage adjustment is necessary.

5.3 Preclinical safety data

Preclinical effects in conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, reproductive studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Joint toxicity was observed at exposure in the human therapeutic range in juvenile rats and dogs. Ofloxacin exhibits a neurotoxic potential and causes reversible testicular alterations at high doses.

Mutagenicity studies showed no evidence for mutagenicity of ofloxacin. However, like some other quinolones Ofloxacin is phototoxic in animals at exposure in the human therapeutic range. The phototoxic, photomutagenic and photocarcinogenic potential of ofloxacin is comparable with that of other gyrase inhibitors.

Preclinical data from conventional genotoxicity studies reveal no special hazard to humans, carcinogen potential has not be investigated.

Reproduction toxicity

Ofloxacin has no effect on fertility, peri- or postnatal development, and therapeutic doses did not lead to any teratogenic or other embryotoxic effects in animals. Ofloxacin crosses the placenta and levels reached in the amniotic fluid are about 30% of the maximal concentrations measured in maternal serum.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Polyvinylpyrrolidone
Colloidal anhydrous silica
Isopropyl alcohol
Methylene dichloride
Magnesium Stearate
Insta moist shield white
MAT SR

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

GFLOX 400 is available as a blister pack of 10 tablets, such one blister is packed in a carton along with pack insert.

6.6 Special precautions for disposal and other Special handling

None

7. Marketed by:

GREENLIFE PHARMACEUTICALS LTD.

2, Bank Lane, Off Town Planning Way,

Ilupeju, lagos,

Nigeria.