1. NAME OF THE MEDICINAL PRODUCT

Brand Name: Remflox 250mg Film-Coated Tablet
Generic Name: Levofloxacin hemihydrate 256.23mg eq. to Levofloxacin 250mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Levofloxacin hemihydrate 256.23mg equivalent to Levofloxacin 250mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Remflox 250mg Film-Coated Tablet is available as light pink coloured oblong film-coated tablets, bisect line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults (more than or equal to 18 years) with mild, moderate and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed as follows.

- Acute maxillary sinusitis due to Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis.
- Acute bacterial exacerbation of chronic bronchitis due to Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenza or Moraxella catarrhalis*).
- Community-acquired pneumonia due to Staphylococcus aureus, Streptococcus pneumoniae, Legionella pneumophila or Mycoplasma pneumoniae.
- Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to Staphylococcus aureus or Streptococcus pyogenes.
- Complicated urinary tract infections (mild to moderate) due to Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis or Pseudomonas aeruginosa*).
- Acute pyelonephritis (mild to moderate) caused by Escherichia coli.

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 levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

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

*Remflox 250mg Film-Coated Tablet should be only used:

- When Pseudomonas is considered AND patient is allergic to antipseudomonal penicillins/ cephalosporins;
- For resistant organisms with no other alternative antibiotics available.

4.2 Posology and method of administration

Administration: Oral

Usual Dose: 250 or 500 mg administered orally as indicated by infection and described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance >80 mL/min). For patients with altered renal function, see Table 2. Oral doses should be administered at least 2 hrs before or 2 hrs after antacids containing magnesium, aluminium, as well as sucralfate, metal cations, such as iron and multivitamin preparations with zinc or didanosine (Videx), chewable/buffered tablets or the pediatric powder for oral solution.

Patients with Normal Renal Function: See Table 1.

Table 1

Infection*	Unit Dose (mg)	Frequency	Duration* (days)	Daily Dose (mg)
Acute bacterial exacerbation of chronic bronchitis	500	Every 24 hrs	7	500
Community-acquired pneumonia	500	Every 24 hrs	7-14	500
Acute maxillary sinusitis	500	Every 24 hrs	10-14	500
Uncomplicated skin and skin structure infections	500	Every 24 hrs	7-10	500
Complicated UTI	250	Every 24 hrs	10	250
Acute pyelonephritis	250	Every 24 hrs	10	250
* Due to the designated pathogens (see Indications).				

Patients with Impaired Renal Function: See Table 2.

Table 2

Renal Status	Initial Dose	Subsequent Dose
Acute bacterial exacerbation of chronic bronchitis/community-acquired pneumonia/acute maxillary sinusitis/uncomplicated skin and skin structure infections.		
CL_{CR} 50-80 mL/min	No dosage adjustment required.	
CL_{CR} 20-49 mL/min	500mg	250mg every 24 hrs
CL_{CR} 10-19 mL/min	500mg	250mg every 48 hrs
Haemodialysis	500mg	250mg every 48 hrs
CAPD	500mg	250mg every 48 hrs
Complicated UTI/acute pyelonephritis.		
CL_{CR} ≥20 mL/min	No dosage adjustment required.	
CL_{CR} 10-19 mL/min	250mg	250mg every 48 hrs
CL_{CR} = Creatinine clearance CAPD = Chronic ambulatory peritoneal dialysis		

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Males:

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

Females:

$$\text{Creatinine Clearance (ml/min)} = \frac{\text{Weight(kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

The serum creatinine should represent a steady state of renal function.

4.3 Contraindications

Persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents or any other components of Remflox 250mg Film-Coated Tablet.

4.4 Special warnings and precautions for use

Fluoroquinolones, including Levofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk of developing fluoroquinolone- associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Patients experiencing pain, swelling, inflammation of a tendon or tendon rupture should be advised to stop taking Levofloxacin and to contact their health care professional promptly about changing their antimicrobial therapy. Patients should also avoid exercise and using the affected area at the first sign of tendon pain, swelling, or inflammation. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid levofloxacin in patients with known history of myasthenia gravis.

The safety and efficacy of levofloxacin in children, adolescents (<18 years), pregnant and nursing women have not been established (see Use in pregnancy, Use in lactation and Use in children under Precautions).

In immature rats and dogs, the oral and i.v. administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species (see Pharmacology under Actions).

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, light headedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia and rarely, suicidal thoughts or acts. These reactions may occur following the 1st dose.

If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction) (see Information for Patients under Precautions, Drug Interactions and Adverse Reactions).

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones including levofloxacin. These reactions often occur following the 1st 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. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other signs of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, i.v. fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated (see Precautions and Adverse Reactions).

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 levofloxacin. 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. Remflox 250mg Film-Coated Tablet should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted (see Information for Patients under Precautions and Adverse Reactions).

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

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of 'antibiotic-associated colitis'.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against C. difficile colitis (see Adverse Reactions).

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

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with preexisting aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids*. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation).

Corticosteroids should not be used if signs of tendinopathy occur.

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Levofloxacin should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section Adverse Effects/Undesirable Effects).

Psychiatric reactions
Psychiatric reactions may occur even after the first administration of fluoroquinolones, including Remflox 250mg Film-Coated Tablet. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see section 'Undesirable effects'). In the event that the patient develops these reactions, Remflox 250mg Film-Coated Tablet should be discontinued and appropriate measures instituted. Caution is recommended if Remflox 250mg Film-Coated Tablet is to be used in psychotic patients or in patients with a history of psychiatric disease.

Precautions
Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance (see Pharmacokinetics under Actions and Dosage & Administration).

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in <0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See Warnings and Drug Interactions.) As with other quinolones, disturbances of blood glucose, including symptomatic hyper and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a

hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately (see Drug Interactions and Adverse Reactions).

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram (see Electrocardiogram under Actions) and infrequent cases of arrhythmia. During post-marketing surveillance, very rare cases of torsade de pointes have been reported in patients taking levofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class Ia or class Ill antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsade de pointes, such as hypokalemia, significant bradycardia and cardiomyopathy should be avoided.

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic and hematopoietic, is advisable during therapy (see Warnings and Adverse Reactions).

Information for Patients: Patients should be advised: to drink fluids liberally; that antacids containing magnesium or aluminum, as well as sucralfate, metal cations, e.g. iron, and multivitamin preparations with zinc or didanosine (Videx) chewable/buffered tablets or the pediatric powder for oral solution should be taken at least 2 hrs before or 2 hrs after oral levofloxacin administration (see Drug Interactions); that oral levofloxacin can be taken without regard to meals; to discontinue treatment and inform the physician if the patient experiences pain, inflammation or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded; that levofloxacin may be associated with hypersensitivity reactions, even following the 1st dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction (see Warnings and Adverse Reactions); to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs; that if diabetic and being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, levofloxacin should be discontinued and consult a physician (see Drug Interactions); that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin; that convulsions have been reported in patients taking quinolones, including levofloxacin and to notify their physician before taking Remflox 250mg Film-Coated Tablet if there is a history of this condition.

Use in children: Safety and effectiveness in pediatric patients and adolescents <18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species (see Warnings).

Use in the elderly: In phase 3 clinical trials, 1190 levofloxacin-treated patients (25%) were more than or equal to 65 years. Of these, 675 patients (14%) were between 65 and 74 years, and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However, since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to levofloxacin may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids, Sucralfate, Metal Cations and Mufti-vitamins: Tablet: While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of Remflox 250mg Film-Coated Tablet with antacids containing magnesium or aluminium, as well as sucralfate, metal cations, such as iron, and multivitamin preparations with zinc, may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminium, as well as sucralfate, metal cations, such as iron and multivitamins preparations with zinc or didanosine (Videx) chewable/buffered tablets or the paediatric powder for oral solution may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least 2 hrs before or 2 hrs after levofloxacin administration.

Nonsteroidal Anti-Inflammatory Drugs: The concomitant administration of a nonsteroidal antiinflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures (see Warnings and Precautions: General).

Antidiabetic Agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co administered.

4.6 Pregnancy and lactation

Carcinogenicity, Mutagenicity & Impairment of Fertility: In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (S. typhimurium and E. coli), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid

exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 rng/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and i.v. doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

Use in pregnancy: There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies potential risk to the fetus (see Warnings).

Use in lactation: Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Patients should be advised that levofloxacin may cause neurological adverse effects (e.g., dizziness, light headedness) and they should know how to react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination (see Warnings and Adverse Reactions).

4.8 Undesirable effects

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.3%. Among patients receiving levofloxacin therapy, 3.9% discontinued levofloxacin therapy due to adverse experiences. The overall incidence, type and distribution of adverse events were similar in patients receiving levofloxacin doses of 750 mg once daily compared to patients receiving doses from 250 mg once daily to 500 mg twice daily.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin: Nausea 1.3%, diarrhoea 1%, vaginitis 0.7%, insomnia 0.5%, abdominal pain 0.4%, flatulence 0.4%, pruritus 0.4%, dizziness 0.3%, dyspepsia 0.3%, rash 0.3%, genital moniliasis 0.2%, taste perversion 0.2%, vomiting 0.2%, constipation 0.1%, fungal infection 0.1%, genital pruritus 0.1%, headache 0.1%, moniliasis 0.1%, nervousness 0.1%, erythematous rash 0.1 % and urticaria 0.1%.

In clinical trials, the following events occurred in >3% regardless of drug relationship: Nausea 7.2%, headache 6.4%, diarrhoea 5.6%, insomnia 4.6%, injection site reaction 3.5% and constipation 3.2%.

In clinical trials, the following events occurred in 1-3% of patients, regardless of drug relationship: Dizziness 2.7%, abdominal pain 2.5%, dyspepsia 2.4%, vomiting 2.3%, vaginitis 1.8%, injection

site pain 1.7%, flatulence 1.5%, pain 1.4%, pruritus 1.3%, sinusitis 1.3%, chest pain 1.2%, fatigue 1.2%, rash 1.2%, back pain 1.1%, injection site inflammation 1.1%, rhinitis 1% and taste perversion 1%.

In clinical trials, the following events, of potential medical importance, occurred at a rate of <1%, regardless of drug relationship:
Autonomic Nervous System Disorders: Postural hypotension.
Body as a Whole-General Disorders: Asthenia, edema, fever, malaise, rigors, substernal chest pain and syncope.
General Cardiovascular Disorders: Cardiac failure, circulatory failure, hypertension and hypotension.
Central and Peripheral Nervous System Disorders: Abnormal coordination, coma, convulsions (seizures), hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, paresthesia, paralysis, speech disorder, stupor, tremor and vertigo.
Gastrointestinal System Disorders: Dry mouth, dysphagia, gastroenteritis, G.I. hemorrhage, pancreatitis, pseudomembranous colitis and tongue edema.
Hearing and Vestibular Disorders: Ear disorder (not otherwise specified) and tinnitus.
Heart Rate and Rhythm Disorders: Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, heart block, palpitation, supraventricular tachycardia, tachycardia and ventricular fibrillation.
Liver and Biliary System Disorders: Abnormal hepatic function, cholelithiasis, hepatic coma and jaundice.
Metabolic and Nutritional Disorders: Aggravated diabetes mellitus, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hypokalemia, increased LDH and decreased weight.
Musculoskeletal System Disorders: Arthralgia, arthritis, arthrosis, muscle weakness, myalgia, osteomyelitis, rhabdo-myolysis, synovitis and tendinitis.
Myo-, Endo-, Pericardial and Valve Disorders: Angina pectoris, coronary thrombosis and myocardial infarction.
Neoplasms: Carcinoma.
Other Special Senses Disorders: Parosmia.
Platelet, Bleeding and Clotting Disorders: Abnormal platelets, embolism (blood clot), epistaxis, purpura and thrombocytopenia.
Psychiatric Disorders: Abnormal dreaming, aggressive reaction, agitation, anorexia, anxiety, confusion, delirium, depression, emotional lability, hallucination, impaired concentration, impotence, manic reaction, mental deficiency, nervousness, paranoia, sleep disorder, somnolence and withdrawal syndrome.
Red Blood Cell Disorders: Anemia.
Reproductive Disorders: Ejaculation failure.
Resistance Mechanism Disorders: Fungal infection and genital moniliasis.
Respiratory System Disorders: ARDS, asthma, coughing, dyspnea, haemoptysis, hypoxia, pleural effusion and respiratory insufficiency.
Skin and Appendages Disorders: Erythema nodosum, genital pruritus, increased sweating, skin disorder, skin exfoliation, skin ulceration and urticaria.
Urinary System Disorders: Abnormal renal function, acute renal failure, face edema and haematuria.

Vascular (Extracardiac) Disorders: Cerebrovascular disorder and phlebitis.
Vision Disorders: Abnormal vision, conjunctivitis and diplopia.
White Cell and RES Disorders: Granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, abnormal WBC (not otherwise specified).
In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established. Crystalluria and cylindruria have been reported with other quinolones. The following laboratory abnormalities appeared in 2.2% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.
Blood Chemistry: Decreased glucose.
Hematology: Decreased lymphocytes.

Post-Marketing Adverse Reactions: Additional adverse events reported from worldwide post marketing experience with levofloxacin include: Allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, haemolytic anaemia, multisystem organ failure, increased International Normalized Ratio (INR)/prothrombin time, Stevens-Johnson syndrome, tendon rupture, torsade de pointes and vasodilation, exacerbation of myasthenia gravis.
Musculoskeletal and connective tissue disorders*
Nervous system disorders*
General disorders and administrative site conditions*
Psychiatric disorders*
Eye disorders*
Ear and labyrinth disorders*

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

Psychiatric disorders
Rare: Psychotic reactions (with e.g. hallucination, paranoia), Depression

Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)

Not known (cannot be estimated from available data): Psychotic disorders with self-endangering behavior including suicidal ideation or suicide attempt

4.9 Overdosage and its treatment

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: Ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones,
ATC code: J01MA12

Pharmacology: The main mechanism of action of levofloxacin is inhibition of DNA gyrase. It is 2-fold stronger than that of ofloxacin. There is not much difference between MIC and MBC. The activity of levofloxacin is bactericidal. In the observation of bacterial morphology, bacteriolysis can be seen in the concentration around MIC.
Remflox 250mg Film-Coated Tablet shows clinical efficacy on respiratory tract infections, genitourinary tract infections, biliary tract infections, intestinal tract infections and other various infections in the surgical, gynecological, dermatological, otorhinolaryngological, ophthalmological, and dental and oral surgery fields.

Microbiology: Remflox 250mg Film-Coated Tablet is a broad-spectrum quinolone antibacterial agent containing levofloxacin, optically active (-)-S-form of racemate ofloxacin synthesized by Daiichi Pharmaceutical Co., Ltd. Remflox 250mg Film-Coated Tablet shows broad and potent antibacterial activities against gram-positive bacteria, e.g. *Staphylococcus sp, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus hemolyticus, Enterococcus sp,* and gram-negative bacteria, *e.g. E. coli, Klebsiella, Serratia*, and *Proteus spp, Pseudomonas aeruginosa, Haemophilus influenzae*. Moreover, Remflox 250mg Film-Coated Tablet has antibacterial activities against *Peptostreptococcus sp* of anaerobic bacteria and *Chlamydia trachomatis*.

5.2 Pharmacokinetic properties

Absorption: Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained 1- 2 hrs after oral dosing. The absolute bioavailability of a 500- and 750-mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single i.v. dose of levofloxacin to healthy volunteers, the mean + SD peak plasma concentration attained was 6.2 ± 1.0 µg/mL after a 500-mg dose infused over 60 min and 11.5 ± 4.0 µg/mL after a 750-mg dose infused over 90 min. Oral administration with food slightly prolongs the time to peak concentration by approximately 1 hr and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin can be administered without regard to food.

Distribution: The mean volume of distribution of levofloxacin generally ranges from 74- 112 L after single and multiple 500- or 750-mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hrs after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750- and 500-mg levofloxacin, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5-fold higher than plasma concentrations and ranged from approximately 2.4-11.3 µg/g over a 24-hr period after a single 500-mg oral dose.

In vitro, over a clinically relevant range (1-10 µg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24-38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism: Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hrs, whereas <4% of the dose was recovered in faeces in 72 hrs. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion: Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6-8 hrs following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144-226 mL/min and 96-142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Special Populations:
Geriatric: There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500-mg oral dose of levofloxacin to healthy elderly subjects (66-80 years), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hrs, as compared to approximately 6 hrs in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary.

Paediatric: The pharmacokinetics of levofloxacin in paediatric subjects have not been studied. Gender: There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500-mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hrs, as compared to approximately 6.1 hrs in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustments based on gender alone is not necessary.

Race: The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 nonwhite. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.
Renal Insufficiency: Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50ml/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD. (See Precautions and Dosage & Administration.)

Hepatic Insufficiency: Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment. Bacterial Infection: The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug Interactions: The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate and antacids has been evaluated. (See Drug Interactions.)

Electrocardiogram: In a study of 48 healthy volunteers receiving single doses of levofloxacin 500, 1000 and 1500 mg and placebo, a dose-related increase from baseline to post-dose of average QTc was observed. These changes were not statistically significant from placebo for the 500-mg dose, variably statistically significant for the 1000-mg dose depending on the correction method used and statistically significant for the 1500-mg dose (see Precautions).

5.3 Preclinical Safety Data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Remflox 250mg Film-Coated Tablet contain the following excipients:

For the tablet core:
- Crospovidone
- Hypromellose
- Microcrystalline cellulose
- Sodium stearyl fumarate.

For the tablet coating (Opadry® Pink Complete Film Coating System 02F240040 Pink):
- Hypromellose
- Titanium dioxide E 171
- Talc
- Macrogol
- Yellow ferric oxide E 172
- Red ferric oxide E 172

6.2 Incompatibilities
Not applicable

6.3 Shelf life
5 years

6.4 Special precautions for storage
Do not store above 30°C.
Keep the tablets in blister in the provided carton to protect from light and moisture.

6.5 Nature and contents of container
Unit carton containing 1 blister strip of 10 tablets with printed aluminium foil on one side and PVC clear film on other side.

6.6 Special precautions for disposal and other handling
As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.

7 MANUFACTURED BY
Remington Pharmaceutical Industries (Pvt) Ltd.
18 km Multan Road, Lahore 53800, Pakistan.

8 PRODUCT REGISTRATION HOLDER
Pharmaforte (Malaysia) Sdn Bhd
2, Jalan PJU 3/49,
Sunway Damansara,
47810 Petaling Jaya,
Selangor, Malaysia.

9 DATE OF REVISION OF THE TEXT

March 2025

Font: Times New Roman
Font Size: 7