National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin Tablets

TERLEV 750

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:

Levofloxacin Hemihydrate equivalent to Levofloxacin ……..750mg

For full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

Brownish Pink coloured, oblong shaped film-coated tablets with a break line on one surface 'MICRO' embossed on other surface

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

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

Levofloxacin Tablets/Injection and Oral Solution are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms in the conditions listed in this section.

Culture and susceptibility testing

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 isolates 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**.**

Nosocomial Pneumonia

It is indicated for the treatment of Nosocomial pneumonia due to methicillin-susceptible Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, or Streptococcus pneumoniae. Adjunctive therapy should be used as clinically indicated. Where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

Community-Acquired Pneumonia: 7–14 day Treatment Regimen

Levofloxacin is indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug-resistant Streptococcus pneumoniae [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae.

MDRSP isolates are strains resistant to two or more of the following antibacterials: penicillin (MIC ≥2mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracycline's and trimethoprim/sulfamethoxazole.

Community-Acquired Pneumonia: 5-day Treatment Regimen

Levofloxacin is indicated for the treatment of community-acquired pneumonia due to Streptococcus pneumoniae (excluding multi-drug-resistant strains [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae.

Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

Levofloxacin is indicated for the treatment of acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis.*

Acute Bacterial Exacerbation of Chronic Bronchitis

Levofloxacin is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.

Complicated Skin and Skin Structure Infections

It is indicated for the treatment of complicated skin and skin structure infections due to methicillin-susceptible Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes, or Proteus mirabilis.

Uncomplicated Skin and Skin Structure Infections

It is indicated for the treatment of uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible Staphylococcus aureus, or Streptococcus pyogenes.

Chronic Bacterial Prostatitis

It is indicated for the treatment of chronic bacterial prostatitis due to Escherichia coli, Enterococcus faecalis, or methicillin-susceptible Staphylococcus epidermidis.

Complicated Urinary Tract Infections: 5-day Treatment Regimen

LEVOFLOXACIN is indicated for the treatment of complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis.*

Complicated Urinary Tract Infections: 10-day Treatment Regimen

Levofloxacin is indicated for the treatment of complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa Clinical Studies.*

Acute Pyelonephritis: 5 or 10-day Treatment Regimen

Levofloxacin is indicated for the treatment of acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia.

Uncomplicated Urinary Tract Infections

Levofloxacin is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*.

Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis. The effectiveness of It is based on plasma concentrations achieved in humans, a surrogate marker considered likely to predict clinical benefit. Levofloxacin has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of Levofloxacin adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged Levofloxacin therapy in adults should only be used when the benefit outweighs the risk.

Plague

Levofloxacin is indicated for treatment of plague, including pneumonic and septicemia plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and pediatric patients, 6 months of age and older

4.2 Posology and method of administration

The usual dose of Levofloxacin Tablets or Oral Solution is 250 mg, 500 mg, or 750 mg administered orally every 24 hours, as indicated by infection and described in Table 1. The usual dose of Levofloxacin Injection is 250 mg or 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in Table 1.

These recommendations apply to patients with creatinine clearance ≥ 50 mL/min. For patients with creatinine clearance <50 mL/min, adjustments to the dosing regimen are required.

Table 1: Dosage in Adult Patients with Normal Renal Function (creatinine clearance ≥ 50 mL/min)

Type of Infection*	Dosed Every 24 hours	Duration (days)†
Nosocomial Pneumonia	750 mg	7 to 14
Community Acquired Pneumonia‡	500 mg‡	7 to 14‡
Community Acquired Pneumonia§	750 mg§	5§

Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7 to 14
Uncomplicated SSSI	500 mg	7 to 10
Chronic Bacterial Prostatitis	500 mg	28
Inhalational Anthrax (Post-Exposure), adult and pediatric patients weighing 50 kg ¶,# or greater	500 mg	60#
Pediatric patients weighing 30 kg to less than 50 kg¶,#		60#
Plague, adult and pediatric patients weighing 50 kg Þ or greater	500 mg	10 to 14
Pediatric patients weighing 30 kg to less than 50 kg		10 to 14
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)S	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)À	250 mg À	10À
Uncomplicated Urinary Tract Infection	250 mg	3
Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)	500 mg	7
Acute Bacterial Sinusitis (ABS)	750 mg	5
	500 mg	10 to 14

Due to the designated pathogens

† Sequential therapy (intravenous Levofloxacin to oral Levofloxacin tablets) may be instituted at the discretion of the healthcare provider.

‡ Due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella*

pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or *Mycoplasma pneumoniae*

§ Due to *Streptococcus pneumonia* (excluding multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae*, *or Chlamydophila pneumoniae.*

¶ Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit.

The safety of Levofloxacin in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients. Prolonged Levofloxacin therapy should only be used when the benefit outweighs the risk.

Þ Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis*. Higher doses of Levofloxacin typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated.

S This regimen is indicated for cUTI due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and AP due to *E. coli*, including cases with concurrent bacteremia.

À This regimen is indicated for cUTI due to *Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa*; and for AP due to *E. coli*.

Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit *[see Clinical Studies (14.9)]*.

ß The safety of Levofloxacin in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients. Prolonged Levofloxacin therapy should only be used when the benefit outweighs the risk.

à Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis*. Higher doses of Levofloxacin typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated.

Dosage in Pediatric Patients

The dosage in pediatric patient's ≥ 6 months of age is described below in Table 2.

Table 2: Dosage in Pediatric Patients ≥ 6 months of age

Pediatric patients weighing 50 kg or greater	Dose	Frequency	Duration†
Inhalational Anthrax (post-exposure)‡,§			
Pediatric patients weighing 50 kg or greater	500 mg	every 24 hours	60 days§
Pediatric patients weighing 30 kg to less than 50 kg	250 mg	every 12 hours	60 days§
Plague¶			
Pediatric patients weighing 50 kg or greater	500 mg	every 24 hours	10 to 14 days
Pediatric patients weighing 30 kg to less than 50 kg	250 mg	every 12 hours	10 to 14 day

Due to *Bacillus anthracis* and *Yersinia pestis*

† Sequential therapy (intravenous Levofloxacin injection to oral Levofloxacin Tablets) may be instituted at the discretion of the healthcare provider.

‡ Begin Levofloxacin Tablets as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*.

§ The safety of Levofloxacin in pediatric patients for durations of therapy beyond 14 days has not been studied. Begin Levofloxacin Tablets as soon as possible after suspected or confirmed exposure to *Yersinia pestis*.

Dosage Adjustment in Adults with Renal Impairment

Administer Levofloxacin with caution in patients with renal impairment. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of Levofloxacin may be reduced in these patients.

In patients with renal impairment (creatinine clearance less than 50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of Levofloxacin due to decreased clearance. No adjustment is necessary for patients with a creatinine clearance greater than or equal to 50 mL/minute.
Table 3 shows how to adjust dose based on creatinine clearance.
Dosage Adjustment in Adult Patients with Renal Impairment (Creatinine Clearance less than 50 mL/minute)

Dosage in Normal Renal Function Every 24 hours	**Creatinine Clearance 20 to 49 mL/minute**	**Creatinine Clearance 10 to 19 mL/minute**	**Hemodialysis or Chronic Ambulatory Peritoneal Dialysis (CAPD)**
750 mg	750 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours
500 mg	500 mg initial dose, then 250 mg every 24 hours	500 mg initial dose, then 250 mg every 48 hours	500 mg initial dose, then 250 mg every 48 hours
250 mg	No dosage adjustment required	250 mg every 48 hours. If treating uncomplicated UTI, then no dosage adjustment is required	No information on dosing adjustment is available

Drug Interaction with Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

Levofloxacin Tablets should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable/buffered tablets or the pediatric powder for oral solution.

Important Administration Instructions

Levofloxacin Tablets can be administered without regard to food.
If patients miss a dose, they should take it as soon as possible anytime up to 8 hours prior to their next scheduled dose. If less than 8 hours remain before the next dose, wait until their next scheduled dose.

Hydration for Patients Receiving Levofloxacin Tablets

Adequate hydration of patients receiving Levofloxacin should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones

4.3 Contraindications

Levofloxacin is contraindicated in persons with known hypersensitivity to Levofloxacin, or other quinolone antibacterial.

4.4 Special warnings and precautions for use

Tendinopathy and Tendon Rupture

Fluoroquinolones, including Levofloxacin 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 been reported 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. Levofloxacin 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.

Exacerbation of Myasthenia Gravis

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

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including Levofloxacin. These reactions often 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. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. 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 Reactions

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 fluoroquinolones, 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.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.

Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with Levofloxacin. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity

were not associated with hypersensitivity**.** The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

Central Nervous System Effects

Convulsions and toxic psychoses have been reported in patients receiving fluoroquinolones, including Levofloxacin. Fluoroquinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving Levofloxacin the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, Levofloxacin should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction**.**

Clostridium difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Levofloxacin, 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. Hyper toxin 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

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 fluoroquinolones, including Levofloxacin. It should be discontinued if the patient experiences symptoms

of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

Prolongation of the QT Interval

Some fluoroquinolones, including Levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during postmarketting surveillance in patients receiving fluoroquinolones, including Levofloxacin. It should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Levofloxacin is indicated in pediatric patients (≥6 months of age) only for the prevention of inhalational anthrax (post-exposure). An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendonopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving Levofloxacin.

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species.

Blood Glucose Disturbances

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with Levofloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) 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. It should be discontinued and appropriate therapy should be initiated immediately.

Photosensitivity/Photo toxicity

Moderate to severe photosensitivity/photo toxicity 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 the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/photo toxicity occurs.

Development of Drug Resistant Bacteria

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

4.5 Interaction with other medicinal products and other forms of interaction

Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

While the chelation by divalent cations is less marked than with other fluoroquinolones, concurrent administration of Levofloxacin Tablets with antacids containing magnesium, or aluminum, 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, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or didanosine may substantially interfere with the gastrointestinal absorption of Levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after oral Levofloxacin administration.

Warfarin

No significant effect of Levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on Levofloxacin absorption and disposition was observed. However, there have been reports during the postmarketting experience in patients that Levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and Levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International

Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if Levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Antidiabetic Agents

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

Non-Steroidal Anti-Inflammatory Drugs

The concomitant administration of a non-steroidal anti-inflammatory drug with a fluoroquinolone, including Levofloxacin may increase the risk of CNS stimulation and convulsive seizures.

Theophylline

No significant effect of Levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of theophylline on Levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when Levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels.

Cyclosporine

No significant effect of Levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other fluoroquinolones. Levofloxacin Cmax and ke were slightly lower while Tmax and t½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for Levofloxacin or cyclosporine when administered concomitantly.

Digoxin

No significant effect of Levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin

absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for Levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the Cmax of Levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and t½ of Levofloxacin were higher while CL/F and CLR were lower during concomitant treatment of Levofloxacin with probenecid or cimetidine compared to Levofloxacin alone. However, these changes do not warrant dosage adjustment for Levofloxacin when Probenecid or cimetidine is co-administered.

Interactions with Laboratory or Diagnostic Testing

Some fluoroquinolones, including Levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Category C. Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

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

Lactation

Based on data on other fluoroquinolones and very limited data on LEVOFLOXACIN, 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.

Pediatric Use

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species.

Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as Levofloxacin. 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 Levofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue Levofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur *[see Boxed Warning*; *Warnings and Precautions (5.1); and Adverse Reactions (6.3)]*.

In phase 3 clinical trials, 1,945 Levofloxacin-treated patients (26%) were ≥ 65 years of age. Of these, 1,081 patients (14%) were between the ages of 65 and 74 and 864 patients (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with Levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using Levofloxacin with concomitant 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 torsade de pointes (e.g., known QT prolongation, uncorrected hypokalaemia).

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 this drug 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.

Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither haemodialysis 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 haemodialysis or CAPD.

Hepatic Impairment

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.

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) 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).

4.8 Undesirable effects

Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Tendon Effects
- Exacerbation of Myasthenia Gravis
- Hypersensitivity Reactions
- Other Serious and Sometimes Fatal Reactions
- Hepatotoxicity
- Central Nervous System Effects
- Clostridium difficile-Associated Diarrhea
- Peripheral Neuropathy that may be irreversible

- Prolongation of the QT Interval
- Musculoskeletal Disorders in Pediatric Patients
- Blood Glucose Disturbances
- Photosensitivity/Photo toxicity
- Development of Drug Resistant Bacteria

Hypotension has been associated with rapid or bolus intravenous infusion of Levofloxacin. Levofloxacin should be infused slowly over 60 to 90 minutes, depending on dosage

Crystalluria and cylindruria have been reported with quinolones, including Levofloxacin. Therefore, adequate hydration of patients receiving Levofloxacin should be maintained to prevent the formation of highly concentrated urine

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Levofloxacin 7537 patients in 29 pooled Phase 3 clinical trials. The population studied had a mean age of 50 years (approximately 74% of the population was < 65 years of age), 50% were male, 71% were Caucasian, 19% were Black. Patients were treated with Levofloxacin for a wide variety of infectious diseases. Patients received Levofloxacin doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3–14 days, and the mean number of days on therapy was 10 days.

The overall incidence, type and distribution of adverse reactions was similar in patients receiving Levofloxacin doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of Levofloxacin due to adverse drug reactions occurred in 4.3% of patients overall, 3.8% of patients treated with the 250 mg and 500 mg doses and 5.4% of patients treated with the 750 mg dose. The most common adverse drug reactions leading to discontinuation with the 250 and 500 mg doses were gastrointestinal (1.4%), primarily nausea (0.6%); vomiting (0.4%); dizziness (0.3%); and headache (0.2%). The most common adverse drug reactions leading to discontinuation with the 750 mg dose were gastrointestinal (1.2%), primarily nausea (0.6%), vomiting (0.5%); dizziness (0.3%); and headache (0.3%).

Adverse reactions occurring in ≥1% of Levofloxacin-treated patients and less common adverse reactions, occurring in 0.1 to <1% of Levofloxacin-treated patients, are shown in Table 4 and Table 5, respectively.

The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, constipation, and dizziness.

Common (≥1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin*

System/Organ Class	Adverse Reaction	% (N=7537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia†	4
Nervous System Disorders		
	headache	6
	dizziness	3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea	1
Gastrointestinal Disorders	nausea	7
	diarrhea	5
	constipation	3
	abdominal pain	2
	vomiting	2
	dyspepsia	2
Skin and Subcutaneous Tissue Disorders	rash	2
	pruritus	1
Reproductive System and Breast Disorders	Vaginitis	1‡
General Disorders and Administration Site Conditions	edema	1
	injection site reaction	1
	chest pain	1

* pool of studies included IV and oral administration

† N = 7274

‡ N = 3758 (women)

Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin (N = 7537)

System/Organ Class	**Adverse Reaction**
Infections and Infestations	genital moniliasis
Blood and Lymphatic System Disorders	anemia thrombocytopenia granulocytopenia
Immune System Disorders	allergic reaction
Metabolism and Nutrition Disorders	hyperglycemia hypoglycemia hyperkalemia
Psychiatric Disorders	anxiety agitation confusion depression hallucination nightmare* sleep disorder* anorexia abnormal dreaming*
Nervous System Disorders	tremor convulsions paresthesia vertigo hypertonia hyperkinesia's

	abnormal gait somnolence* syncope
Respiratory, Thoracic and Mediastinal Disorders	epistaxis
Cardiac Disorders	cardiac arrest palpitation ventricular tachycardia ventricular arrhythmia
Vascular Disorders	phlebitis
Gastrointestinal Disorders	gastritis stomatitis pancreatitis esophagitis gastroenteritis glossitis pseudomembranous/ *C. difficile* colitis
Hepatobiliary Disorders	abnormal hepatic function increased hepatic enzymes increased alkaline phosphatase
Skin and Subcutaneous Tissue Disorders	urticaria
Musculoskeletal and Connective Tissue Disorders	arthralgia tendinitis myalgia skeletal pain
Renal and Urinary Disorders	abnormal renal function acute renal failure

* N = 7274

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with quinolones, including Levofloxacin. The relationship of the drugs to these events is not presently established.

Postmarketting Experience

Table 6 lists adverse reactions that have been identified during post-approval use of Levofloxacin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketting Reports Of Adverse Drug Reactions

System/Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	pancytopenia aplastic anemia leukopenia hemolytic anemia eosinophilia
Immune System Disorders	hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions anaphylactic shock angioneurotic edema serum sickness
Psychiatric Disorders	psychosis paranoia isolated reports of suicidal ideation, suicide attempt and completed suicide
Nervous System Disorders	exacerbation of myasthenia gravis anosmia

System/Organ Class	Adverse Reaction
	ageusia parosmia dysgeusia peripheral neuropathy (may be irreversible) isolated reports of encephalopathy abnormal electroencephalogram (EEG) dysphonia pseudo tumor cerebri
Eye Disorders	uveitis vision disturbance, including diplopia visual acuity reduced vision blurred scotoma
Ear and Labyrinth Disorders	hypoacusis tinnitus
Cardiac Disorders	isolated reports of torsade de pointes electrocardiogram QT prolonged tachycardia
Vascular Disorders	vasodilatation
Respiratory, Thoracic and Mediastinal Disorders	isolated reports of allergic pneumonitis
Hepatobiliary Disorders	hepatic failure (including fatal cases) hepatitis jaundice
Skin and Subcutaneous Tissue Disorders	bullous eruptions to include: Stevens-Johnson Syndrome

System/Organ Class	Adverse Reaction
	toxic epidermal necrolysis Acute Generalized Exanthematous Pustulosis (AGEP) fixed drug eruptions erythema multiforme photosensitivity/photo toxicity reaction leukocytoclastic Vasculitis
Musculoskeletal and Connective Tissue Disorders	tendon rupture muscle injury, including rupture rhabdomyolysis
Renal and Urinary Disorders	interstitial nephritis
General Disorders and Administration Site Conditions	multi-organ failure pyrexia
Investigations	prothrombin time prolonged international normalized ratio prolonged muscle enzymes increased

4.9 Overdose

In the event of an acute over dosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

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 IV produced significant mortality in rodents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infective for systemic use – Antibacterials for systemic use – Quinolone antibacterials Fluoroquinolones

ATC code: J01MA12

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of Levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Drug Resistance

Fluoroquinolones resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV, termed the Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including Levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to Levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10-9 to 10-10). Although cross-resistance has been observed between Levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to Levofloxacin.

Activity in vitro and in vivo

Levofloxacin has in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms.

Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Levofloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described

Aerobic Gram-Positive Microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP])
Streptococcus pyogenes

MDRSP (Multi-drug resistant Streptococcus pneumoniae) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime; macrolides, tetracycline and trimethoprim/sulfamethoxazole.

Aerobic Gram-Negative Microorganisms
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

As with other drugs in this class, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with Levofloxacin.

Other Microorganisms
Chlamydophila pneumoniae
Mycoplasma pneumoniae

Levofloxacin has been shown to be active against Bacillus anthracis both in vitro and by use of plasma levels as a surrogate marker in a rhesus monkey model for anthrax (post-exposure).

The following in vitro data are available, but their clinical significance is unknown: Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of Levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms
Staphylococcus haemolyticus
B-hemolytic Streptococcus (Group C/F)

B-hemolytic Streptococcus (Group G)
Streptococcus agalactiae
Streptococcus milleri
Viridans group streptococci
Aerobic Gram-Negative Microorganisms
Acinetobacter baumannii
Acinetobacter lwoffii
Bordetella pertussis
Citrobacter koseri
Citrobacter freundii
Enterobacter aerogenes
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Pantoea agglomerans
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Anaerobic Gram-Positive Microorganisms
Clostridium perfringens
Susceptibility Tests

Susceptibility testing for Levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method1 (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of Levofloxacin powder. The MIC values should be interpreted according to the criteria.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure2 requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg Levofloxacin to test the susceptibility of microorganisms to Levofloxacin.

5.2 Pharmacokinetic properties

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of Levofloxacin from a 500 mg tablet and a 750 mg tablet of Levofloxacin are both approximately 99%, demonstrating complete oral absorption of Levofloxacin. Following a single intravenous dose of Levofloxacin to healthy volunteers, the mean ±SD peak plasma concentration attained was 6.2 ±1.0 mcg/mL after a 500 mg dose infused over 60 minutes and 11.5 ±4.0 mcg/mL after a 750 mg dose infused over 90 minutes.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2 mcg/mL after the 500 mg doses, and 8.6 ±1.9 and 1.1 ±0.4 mcg/mL after the 750 mg doses, respectively. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily IV regimens were approximately 6.4 ±0.8 and 0.6 ±0.2 mcg/mL after the 500 mg doses, and 12.1 ±4.1 and 1.3 ±0.71 mcg/mL after the 750 mg doses, respectively. Oral administration of a 500 mg dose of Levofloxacin with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, Levofloxacin Tablets can be administered without regard to food. It is recommended that LEVOFLOXACIN Oral Solution be taken 1 hour before or 2 hours after eating.

The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for LEVOFLOXACIN Tablets when equal doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable.

Figure 2: Mean Levofloxacin Plasma Concentration vs. Time Profile: 750 mg

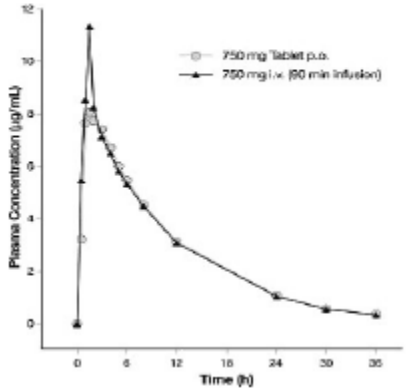
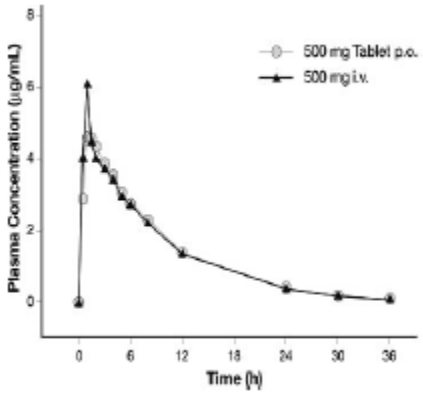


Figure 3: Mean Levofloxacin Plasma Concentration vs. Time Profile: 500 mg



Distribution

The mean volume of distribution of Levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg 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 hours 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 administrations of 750 mg and 500 mg doses of 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 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 mcg/mL) of serum/plasma Levofloxacin concentrations, Levofloxacin is approximately 24 to 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 stereo chemically 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 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. 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 to 8 hours following single or multiple doses of Levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 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.

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 of age), the mean terminal plasma elimination half-life of Levofloxacin was about 7.6 hours, as compared to approximately 6 hours 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.

Pediatrics

The pharmacokinetics of Levofloxacin following a single 7 mg/kg intravenous dose were investigated in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared Levofloxacin faster than adult patients, resulting in lower plasma exposures than adults for a given mg/kg dose. Subsequent

pharmacokinetic analyses predicted that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures (AUC0–24 and Cmax) to those observed in adult patients administered 500 mg of Levofloxacin once every 24 hours.

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 hours, as compared to approximately 6.1 hours 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 adjustment 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 non-whites. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal Impairment

Clearance of Levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/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.

Hepatic Impairment

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-Drug Interactions

The potential for pharmacokinetic drug interactions between LEVOFLOXACIN and antacids, warfarin, theophylline, cyclosporine, digoxin, probenecid, and cimetidine has been evaluated.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

dietary administration for 2 years; the highest dose (100 mg/kg/day*)* was 1.4 times the Maximum Recommended Human Dose (MRHD) (750 mg) after normalization for total body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any Levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal Levofloxacin concentrations in the hairless mice ranged from 25 to 42 mcg/g at the highest Levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal Levofloxacin concentrations in human subjects receiving 750 mg of Levofloxacin averaged approximately 11.8 mcg/g at Cmax.

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 mg/kg/day, corresponding to 4.2 times the MRHD and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the MRHD after normalization for total body surface area.

Animal Toxicology and/or Pharmacology

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. In immature dogs (4–5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of Levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with Levofloxacin

at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine (dosing was terminated in the low and mid-dose groups on Day 9 due to similar findings at the mid-dose). Slight musculoskeletal clinical effects, in the absence of gross pathological or Histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels. The low and mid-dose groups in that study were also evaluated by electron microscopy, revealing compound-related ultra structural effects in articular cartilage chondrocytes at the end of treatment and at the end of recovery in both of those doses.

When tested in a mouse ear swelling bioassay, Levofloxacin exhibited photo toxicity similar in magnitude to ofloxacin, but less photo toxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, Levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

In vitro and *in vivo* studies in animals indicate that Levofloxacin is neither an enzyme inducer nor inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Povidone (K-30)

Croscarmellose sodium

Magnesium stearate

Talc

Hypromellose

Ferric oxide RED

Talc

Titanium dioxide

Propylene glycol

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Not applicable

6.5 Nature and contents of container

1x10s, Alu/Alu Blister

6.6 Special precautions for disposal and other handling

No Special requirement

7. Marketing Authorization Holder

MICRO LABS LIMITED

31, Race course road

Bangalore-560001

8. Number from the register of medicinal product.

Not applicable

9. Date of authorization or of the last renewal of the authorization

Not applicable

10. Date of revision of text

July 2021