LEVOFLOXACIN TABLETS 750mg
LEVOBACT-750

13. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Levofloxacin Tablets

13.1 Strength:

750mg

13.2 Pharmaceutical form

Tablets for oral administration

14. Quality and Quantitative Composition

Each film-coated tablet contains:
Levofloxacin Hemihydrate
Equivalent to Levofloxacin 750mg

15. Pharmaceutical Form

Tablets

16. Clinical Particulars

16.1 Therapeutic indications

Levofloxacin tablets are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- Nosocomial Pneumonia
- Community-Acquired Pneumonia: 7–14 day Treatment Regimen
- Community-Acquired Pneumonia: 5-day Treatment Regimen
- Complicated Skin and Skin Structure Infections
- Uncomplicated Skin and Skin Structure Infections
- Chronic Bacterial Prostatitis
- Inhalational Anthrax (Post-Exposure)
- **Plague**
- Complicated Urinary Tract Infections: 5-day Treatment Regimen
- Complicated Urinary Tract Infections: 10-day Treatment Regimen
- Acute Pyelonephritis: 5 or 10-day Treatment Regimen
- Uncomplicated Urinary Tract Infections

- Acute Bacterial Exacerbation of Chronic Bronchitis
- Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

16.2 Posology and method of administration

The usual dose of Levofloxacin Tablets is 250 mg, 500 mg, or 750 mg administered orally every 24 hours, as indicated by infection and described in Table 1.

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

Dosage of Levofloxacin Tablets in Adult Patients with Creatinine Clearance greater than or equal to 50 mL/minute)

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¶,#	see TABLE 2below (2.2)	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	see TABLE 2below (2.2)	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 pneumoniae* (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*.

Dosage of Levofloxacin Tablets in Pediatric Patients with Inhalational Anthrax or Plague

The dosage of Levofloxacin Tablets for inhalational anthrax (post-exposure) and plague in pediatric patients who weigh 30 kg or greater is described below in Table 2. Levofloxacin Tablets cannot be administered to patients who weigh less than 30 kg because of the limitations of the available strength. Alternative formulations of levofloxacin may be considered for pediatric patients who weigh less than 30 kg.

Type of Infection*	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 days

* 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: Dosage Adjustment in Adult Patients with Renal Impairment (Creatinine Clearance less than 50 mL/minute)

Creatinine Clearance greater than or equal to 50 mL/minute	Creatinine Clearance 20 to 49 mL/minute	Creatinine Clearance 10 to 19 mL/minute	Hemodialysis or Chronic Ambulatory Peritoneal Dialysis (CAPD)
750 mg every 24 hours	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 every 24 hours	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 every 24 hours	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, aluminium, 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.

Administration Instructions

Levofloxacin Tablets can be administered without regard to food.

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

16.3 Method of administration

For oral use

The usual dose of Levofloxacin Tablets is 250 mg, 500 mg, or 750 mg administered orally every 24 hours

16.4 Contraindications

Levofloxacin is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials

16.5 Special warning and precautions

Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects

Fluoroquinolones, including Levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting Levofloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue Levofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including Levofloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Tendinitis and Tendon Rupture

Fluoroquinolones, including Levofloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages . This adverse reaction most frequently involves the Achilles tendon and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites. Tendinitis or tendon rupture can occur within hours or days of starting Levofloxacin or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors 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. Discontinue Levofloxacin immediately 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. Avoid Levofloxacin in patients who have a history of tendon disorders or tendon rupture.

Peripheral Neuropathy

Fluoroquinolones, including Levofloxacin, have been associated with an increased risk of peripheral neuropathy. 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. Symptoms may occur soon after initiation of Levofloxacin and may be irreversible in some patients.
Discontinue Levofloxacin immediately 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. Avoid fluoroquinolones, including Levofloxacin, in patients who have previously experienced peripheral neuropathy.

Central Nervous System Effects

Psychiatric Adverse Reactions

Fluoroquinolones, including Levofloxacin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychoses, hallucinations, or paranoia; depression, or suicidal thoughts; anxiety, agitation, restlessness, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. Attempted or completed suicide has been reported, especially in patients with a medical history of depression, or an underlying risk factor for depression. These reactions may occur following the first dose. If these reactions occur in patients receiving Levofloxacin, discontinue Levofloxacin and institute appropriate measures.

Central Nervous System Adverse Reactions

Fluoroquinolones, including Levofloxacin, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (including pseudotumor cerebri), tremors, and lightheadedness. 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). If these reactions occur in patients receiving Levofloxacin, discontinue Levofloxacin and institute appropriate measures.

Exacerbation of Myasthenia Gravis

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

Other Serious and Sometimes Fatal Adverse Reactions

Other serious and sometimes fatal adverse reactions, 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.

Discontinue Levofloxacin immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and institute supportive measures.

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.

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.

***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. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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. Levofloxacin 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.

Blood Glucose Disturbances

Fluoroquinolones, including Levofloxacin, have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, 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. Severe cases of hypoglycemia resulting in coma or death have been reported. If a hypoglycemic reaction occurs in a patient being treated with Levofloxacin, discontinue Levofloxacin and initiate appropriate therapy 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

Very rarely, patients treated with fluoroquinolone or quinolone antibiotics have suffered long-lasting and disabling side effects, mainly involving muscles, tendons and bones and the nervous system.

Fluoroquinolone and quinolone antibiotics should not be used

- To treat infections that might get better without treatment or are not severe (such as throat infections);
- For preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- To treat patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic;
- To treat mild or moderately severe infections unless other antibacterial medicines commonly recommended for these infections cannot be used;
- Be used with caution especially for the elderly, patients with kidney problems, patients who have had organ transplantation or those who are being treated with a systemic corticosteroid. These patients are at higher risk of tendon injury caused by fluoroquinolone and quinolone antibiotics.

16.6 Paediatric population

Musculoskeletal Disorders in Pediatric Patients

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

16.7 Interaction with other medicinal products and other forms of interactions

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 post marketing 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.

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 fluoroquinolones, 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 k_e 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 C_{max} 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.

16.8 Additional information on special populations

None

16.9 Paediatric population

None

16.10 Fertility, pregnancy and lactation

16.10.1 General principles

16.10.2 Women of childbearing potential / Contraception in males and females

Not known

16.10.3 *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 the potential risk to the fetus.

16.10.4 *Lactation*

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.

16.4.5 ***Fertility***

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

16.11 Effects on ability to drive and use machine

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).

16.12 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%).

16.13 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.

17. Pharmacological Properties
17.1 Pharmacodynamic Properties
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
Yersinia pestis
Clostridium perfringens

17.2 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.

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.

17.3 Preclinical safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative 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 highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

17.4 Environmental Risk Assessment (ERA)
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

18. Pharmaceutical Particulars
18.1 List of excipients
Microcrystalline Cellulose, Povidone, Croscarmellose Sodium, Magnesium Stearate, Talc, Hypromellose, Isopropyl Alcohol, Dichloromethane, Ferric Oxide, Titanium Dioxide, Propylene Glycol.

18.2 Incompatibilities
None

18.3 Shelf life
36 months from the date of manufacturing.

18.4 Special precautions for storage
Store below 30°C. Keep this medicine out of reach of children

18.5 Nature and contents of container
Alu/Alu Blister pack of 10 Tablets, such 3 blisters are packed in printed outer carton along with pack insert.

18.6 Special precautions for disposal and other handling
None

19. Marketing Authorization Holder and Manufacturing Site Addresses
MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur - 635 126 (T.N.)
INDIA

20. Marketing Authorisation Number
---

21. Date of First Registration/Renewal of the registration
---

22. Date of revision of the text
April 2019

23. DOSIMETRY

Not applicable

24. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable