

Asilix

(Levofloxacin)

ایسیلیکس

WARNING

Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

COMPOSITION

Each **Asilix** 250mg film-coated tablet contains 250 mg of levofloxacin.

Each **Asilix** 500mg film-coated tablet contains 500 mg of levofloxacin.

MECHANISM OF ACTION

Asilix (levofloxacin) is a synthetic broad spectrum antibacterial agent for oral administration. 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. 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.

PHARMACOKINETIC

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 a 500 mg tablet is approximately 99%, demonstrating complete oral absorption of levofloxacin. Levofloxacin tablets can be administered without regard to food.

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 once-daily dosage regimen.

Distribution: The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg doses, indicating widespread distribution into body tissues. Levofloxacin is approximately 24 to 38% bound to serum proteins. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism: 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.

SPECIAL POPULATIONS

Geriatric: Levofloxacin dose adjustment based on age alone is not necessary.

Gender: Dose adjustment based on gender alone is not necessary.

Renal insufficiency: 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 insufficiency: Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial infection: The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

MICROBIOLOGY

Aerobic Gram-Positive Microorganisms

Enterococcus faecalis (moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including multi-drug resistant strains)
Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa (some strains may develop resistance fairly rapidly during treatment with **Asilix**).
Serratia marcescens

Other Microorganisms

Chlamydia pneumoniae
Mycoplasma pneumoniae
Levofloxacin has been shown to be active against bacillus anthracis

INDICATIONS

Asilix Tablets are indicated for the treatment of adults (≥ 18 years of age) with mild and moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

- Nosocomial Pneumonia
- Community-Acquired Pneumonia
- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Complicated and uncomplicated skin and skin structure infections

- Chronic bacterial prostatitis
- Complicated and uncomplicated urinary tract infections
- Acute Pyelonephritis
- Inhalational Anthrax (Post-Exposure)

DOSAGE AND ADMINISTRATION

The usual dose of **Asilix** tablets is 250 mg, 500 mg, or 750 mg administered orally every 24 hours, as indicated by infection and described in table below.

The following dose recommendations can be given for **Asilix**:

Dosage in patients with normal renal function: (creatinine clearance $\geq$ 50 ml/min).

Type of Infection	Dosed Every 24 hrs	Duration (days)
Nosocomial Pneumonia	750 mg	7-14
Community Acquired Pneumonia	500 mg	7-14
Community Acquired Pneumonia	750 mg	5
Acute Bacterial Sinusitis	750mg/500mg	5-10/14
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7-14
Uncomplicated SSSI	500 mg	7-10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection or Acute Pyelonephritis	750 mg	5
Complicated Urinary Tract Infection or Acute Pyelonephritis	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Inhalational Anthrax (Post-Exposure)	500 mg	60

Dosage in patients with impaired renal function: (creatinine clearance < 50 ml/min).

Dosage in Normal Renal Function Every 24 hours	Creatinine Clearance 20 to 49 mL/min	Creatinine Clearance 10 to 19 mL/min	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

Asilix tablets can be administered without regard to food.

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

UNDESIRABLE EFFECTS

Very common ($\geq$ 1/10), common ($\geq$ 1/100, <1/10), uncommon ($\geq$ 1/1000, $\leq$ 1/100) rare ($\geq$ 1/10000, $\leq$ 1/1000), very rare ($\leq$ 1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Uncommon: Fungal infection (and proliferation of other resistant microorganisms)

Blood and lymphatic system disorders

Uncommon: Leukopenia, eosinophilia

Rare: Thrombocytopenia, neutropenia

Very rare: Agranulocytosis

Not Known: Pancytopenia, haemolytic anaemia

Immune system disorders

Very rare: Anaphylactic shock

Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

Not known: Hypersensitivity

Metabolism and nutrition disorders

Uncommon: Anorexia

Very rare: Hypoglycemia, particularly in diabetic patients

Psychiatric disorders

Uncommon : Insomnia, nervousness

Rare: Psychotic disorder, depression, confusional state, agitation, anxiety

Very rare : Psychotic reactions with self-endangering behaviour including suicidal ideation or acts, hallucination

Nervous system disorders

Uncommon: Dizziness, headache, somnolence

Rare: Convulsion, tremor, paraesthesia

Very rare: sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia

Eye disorders

Very rare: Visual disturbance

Ear and Labyrinth disorders

Uncommon: Vertigo

Very rare: Hearing impaired

Not known: Tinnitus

Cardiac disorders

Rare: Tachycardia

Not Known: Electrocardiogram QT prolonged

Vascular disorders

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders

Rare: Bronchospasm, dyspnoea

Very rare: Pneumonitis allergic

Gastrointestinal disorders

Common: Diarrhoea, nausea

Uncommon: Vomiting, abdominal pain, dyspepsia, flatulence, constipation.

Rare: Diarrhoea -haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis

Hepatobiliary disorders

Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)

Uncommon: Blood bilirubin increased

Very rare: Hepatitis

Not known: Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases.

Skin and subcutaneous tissue disorders

Uncommon : Rash, pruritus

Rare: Urticaria

Very rare: Angioneurotic oedema, photosensitivity reaction

Not Known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis

Mucocutaneous reactions may sometimes occur even after the first dose

Musculoskeletal and Connective tissue disorders

Rare: Tendon disorder including tendinitis (e.g. Achilles tendon), Arthralgia, Myalgia

Very rare: Tendon rupture. This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with myasthenia gravis

Not Known: Rhabdomyolysis

Renal and urinary disorders

Uncommon: Blood creatinine increased

Very rare: Renal failure acute (e.g. due to nephritis interstitial)

General disorders

Uncommon: Asthenia

Very rare: Pyrexia

Not known: Pain (including pain in back, chest, and extremities)

Other undesirable effects which have been associated with fluoroquinolone administration include:

- Extrapyrimal symptoms and other disorders of muscular coordination, hypersensitivity vasculitis and attacks of porphyria in patients with porphyria

DRUG INTERACTIONS

Antacids, Sucralfate, Metal Cations, Multivitamins: **Asilix** 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 levofloxacin administration.

Theophylline: Concomitant administration of other quinolones 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.

Warfarin: 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. 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.

Cyclosporine: No dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin: No dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine: No dosage adjustment is required for levofloxacin when probenecid or cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

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

INTERACTIONS WITH LABORATORY OR DIAGNOSTIC TESTING

Some quinolones, 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In the most severe cases of pneumococcal pneumonia **Asilix** may not be the optimal therapy. Nosocomial infections due to *P. aeruginosa* may require combination therapy.

Tendinitis and tendon rupture: Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed **Asilix**. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with **Asilix** must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Clostridium difficile-associated disease: Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including **Asilix**, and may range in severity from mild diarrhea to fatal colitis. 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.

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. These reactions may occur following the first dose. If these reactions occur in patients receiving **Asilix**, the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, **Asilix** 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.)

Patients with renal impairment: Since levofloxacin is excreted mainly by the kidneys, the dose of **Asilix** should be adjusted in patients with renal impairment.

Hypersensitivity reactions: Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose. Discontinue treatment immediately and initiate appropriate emergency treatment.

Hypoglycemia: As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitisation: Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists: Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with **Asilix** in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

QT interval prolongation: Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides).
- Uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- Elderly
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Peripheral neuropathy: Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. **Asilix** should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Opiates: In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Hepatotoxicity: Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. **Asilix** should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

PREGNANCY:

Pregnancy Category C.

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.

NURSING MOTHERS

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

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established.

OVERDOSE

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

CONTRAINDICATIONS

- Previous hypersensitivity reactions to levofloxacin, other quinolones, or any other ingredient.
- Epilepsy.
- Patients with a history of tendon disorders associated with fluoroquinolone administration.
- Children or adolescents (under 18 years of age).
- During pregnancy and lactation.

PRESENTATION

Asilix 250mg Tablets: 1 x 10's/pack.

Asilix 500mg Tablets: 1 x 10's/pack.

Dosage:

As directed by the physician.

Instructions:

Store below 30°C.

Protect from sunlight & moisture.

Keep out of reach of children.

خوراک:

ڈاکٹر کی ہدایت کے مطابق۔

ہدایات:

دوا کو 30°C سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

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Detailed prescribing information is available on request.