Levoscot Tablets*

لیووسکاٹ ٹیبلٹس

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS.

- Fluoroquinolones, including Levofloxacin, have been associated with disabling and potentially irreversible serious adverse reaction that have occurred together, including:

o Tendinitis and tendon rupture

o Peripheral Neuropathy

o Central Nervous System effects

Discontinue Levofloxacin immediately and avoid the use of Fluoroquinolones, including Levofloxacin in patients who experience any of these serious adverse reactions.

- Fluoroquinolones, including Levofloxacin may exacerbate muscle weakness in patients with myasthenia gravis. Avoid Levofloxacin in patients with known history of myasthenia gravis.
- As Fluoroquinolones, including Levofloxacin have been associated with serious adverse reactions, reserve Levofloxacin for use in patients who have no alternative treatment options for the following indications:

o Acute exacerbation of chronic bronchitis

o Acute sinusitis

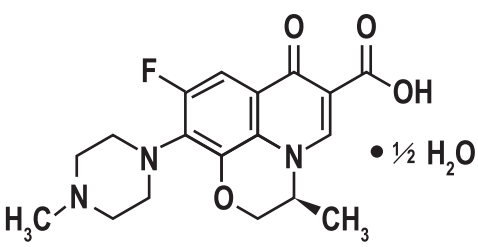
o Acute uncomplicated cystitis

COMPOSITION

Each tablet contains: Levofloxacin Hemihydrate eq. to Levofloxacin USP…….....
250 & 500 mg, respectively.

DESCRIPTION

LEVOSCOT (Levofloxacin) is a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name of Levofloxacin is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitter ion at the pH conditions in the small intestine. Levofloxacin has the potential to form stable coordination compounds with many metal ions. The empirical formula is $C_{18}H_{20}FN_3O_4 \cdot ½\ H_2O$, the molecular weight is 370.38 and its chemical structure is as follows:



CLINICAL PHARMACOLOGY

Mechanism of Action: Levofloxacin is a member of the fluoroquinolone class of antibacterial agents. 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, enzymes required for DNA replication, transcription, repair and recombination.

Pharmacokinetics:

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 is approximately 99%, demonstrating complete oral absorption of levofloxacin. LEVOSCOT 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 doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid at approximately 3 hours after dosing. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations are generally 2-to 5-fold higher than plasma concentrations and range from approximately 2.4 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose. Levofloxacin is mainly bound to serum albumin. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism: Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose recovers as unchanged drug in urine within 48 hours, whereas less than 4% of the dose recovers in feces in 72 hours. Less than 5% of an administered dose recovers in the urine as the desmethyl and N-oxide metabolites. 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. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively.

INDICATIONS AND USAGE

LEVOSCOT Tablets 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 below:

Nosocomial Pneumonia: LEVOSCOT 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: LEVOSCOT 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*.

Community-Acquired Pneumonia; 5-day Treatment Regimen: LEVOSCOT is indicated for the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* (excluding multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae.*

Complicated Skin and Skin Structure Infections: LEVOSCOT 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: LEVOSCOT 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: LEVOSCOT is indicated for the treatment of chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or methicillin-susceptible *Staphylococcus epidermidis*.

Inhalational Anthrax (Post-Exposure): LEVOSCOT is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. Prolonged LEVOSCOT therapy should only be used when the benefit outweighs the risk.

Plague: LEVOSCOT is indicated for treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis* and prophylaxis for plague in adults and pediatric patients, 6 months of age and older.

Complicated Urinary Tract Infections; 5-day Treatment Regimen: LEVOSCOT 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: LEVOSCOT 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.*

Acute Pyelonephritis; 5 or 10-day Treatment Regimen: LEVOSCOT is indicated for the treatment of acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia.

Uncomplicated Urinary Tract Infections: LEVOSCOT is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*. Because fluoroquinolones, including LEVOSCOT, have been associated with serious adverse reactions and for some patients uncomplicated urinary tract infection is self-limiting, reserve LEVOSCOT for treatment of uncomplicated urinary tract infections in patients who have no alternative treatment options.

Acute Bacterial Exacerbation of Chronic Bronchitis: LEVOSCOT is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.

Because fluoroquinolones, including LEVOSCOT, have been associated with serious adverse reactions and for some patients ABECB is self-limiting, reserve LEVOSCOT for treatment of ABECB in patients who have no alternative treatment options.

Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens: LEVOSCOT is indicated for the treatment of acute bacterial sinusitis (ABS) due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis*. Because fluoroquinolones, including LEVOSCOT, have been associated with serious adverse reactions and for some patients ABS is self-limiting, reserve LEVOSCOT for treatment of ABS in patients who have no alternative treatment options.

CONTRAINDICATIONS

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

ADVERSE REACTIONS

Serious and Otherwise Important Adverse Reactions: Following are the serious and otherwise important adverse drug reactions that are Disabling and Potentially Irreversible Serious Adverse Reactions:

- Tendinitis and Tendon Rupture
- Peripheral Neuropathy
- Central Nervous System Effects
- Exacerbation of Myasthenia Gravis
- Other Serious and Sometimes Fatal Reactions
- Hypersensitivity Reactions
- Hepatotoxicity
- *Clostridium difficile*-Associated Diarrhea
- Prolongation of the QT Interval
- Musculoskeletal Disorders in Pediatric Patients
- Blood Glucose Disturbances
- Photosensitivity/Phototoxicity
- Development of Drug Resistant Bacteria

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

DRUG INTERACTIONS

Chelating Agents: ***Antacids, Sucralfate, Metal Cations, Multivitamins:*** Concurrent administration of LEVOSCOT 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. These agents should be taken at least two hours before or two hours after oral LEVOSCOT administration. **Warfarin:** 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 NSAIDs with a fluoroquinolone, including LEVOSCOT, may increase the risk of CNS stimulation and convulsive seizures. **Theophylline:** Theophylline levels should be closely monitored and appropriate dosage adjustments made when LEVOSCOT is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels.

USE IN SPECIFIC POPULATION

Pregnancy: Pregnancy Category C. LEVOSCOT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Levofloxacin is excreted in human milk. Because of the potential for serious adverse reactions from LEVOSCOT 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 below the age of six months have not been established. **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. Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with levofloxacin in patients 65 years of age or older. LEVOSCOT 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. **Renal Impairment:** Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (CLcr <50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis is effective in removal of levofloxacin from the body.

WARNINGS AND PRECAUTIONS

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. **Peripheral Neuropathy:** Fluoroquinolones, including levofloxacin, have been associated with an increased risk of peripheral neuropathy. 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. **Central Nervous System Effects:** Fluoroquinolones, including levofloxacin, have been associated with an increased risk of CNS effects, including convulsions, toxic psychoses, increased intracranial pressure. Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, and insomnia. Suicidal thoughts, and attempted or completed suicide may also occur, 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 discontinue levofloxacin. **Exacerbation of Myasthenia Gravis:** Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. **Hypersensitivity Reactions:** Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. **Hepatotoxicity:** The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis. ***Clostridium difficile*-Associated Diarrhea:** *Clostridium difficile*-associated diarrhea has been reported with use of nearly all antibacterial agents, including levofloxacin and may range in severity from mild diarrhea to fatal colitis. **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. 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. **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 risk of musculoskeletal disorders) is associated with pediatric patients receiving levofloxacin. **Blood Glucose Disturbances:** As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper-and hypoglycemia, is associated with levofloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent or with insulin. In these patients, careful monitoring of blood glucose is recommended. **Photosensitivity/Phototoxicity:** Moderate to severe photosensitivity/phototoxicity reactions 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.

DOSAGE AND ADMINISTRATION

Dosage in Adult Patients with Normal Renal Function: The usual dose of LEVSCOT Tablets is 250 mg, 500 mg, or 750 mg administered orally every 24 hours, as indicated by infection and described in Table 1.

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

Indication	Daily Dose	Duration (Days)
Nosocomial Pneumonia	750 mg	7-14
Community Acquired Pneumonia	500 mg	7-14
	750 mg	5
Complicated Skin and Skin Structure Infections	750 mg	7-14
Uncomplicated Skin and Skin Structure Infections	500 mg	7-10
Chronic Bacterial Prostatitis	500 mg	28
Inhalational Anthrax (Post-Exposure) (Patients>50 kg)	500 mg	60
Plague (Patients >50 kg)	500 mg	10 to 14
Complicated Urinary Tract Infection or Acute Pyelonephritis	750 mg	5
	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10-14

Dosage in Pediatric Patients: The dosage in pediatric patients ≥ 6 months of age is described below in Table 2.

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

Indication	Dose	Frequency Once every	Duration (Days)
Inhalational Anthrax (post-exposure)			
Pediatric patients >50 kg	500 mg	24 hour	60
Pediatric patients<50 kg and 6 months of age	8 mg/kg (Not 250 mg per dose)	12 hour	60
Plague			
Pediatric patients >50 kg	500 mg	24 hour	10 to 14
Pediatric patients < 50 kg and 6 months of age	8 mg/kg (Not 250 mg per dose)	12 hour	10 to 14

Dosage Adjustment in Adults with Renal Impairment: In patients with impaired renal function (CLcr <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. Table 3 shows how to adjust dose based on creatinine clearance.

Table 3: Dosage Adjustment in Adult Patients with Renal Impairment (CLcr 50 mL/min)

Dosage in Normal Renal Function Every 24 hours	CLcr 20 to 49 mL/min	CLcr 10 to 19 mL/min	Hemodialysis or Chronic Ambulatory Peritoneal Dialysis
250 mg	No dosage adjustment is required.	250 mg every 48 hours. If treating uncomplicated UTI, then no dosage adjustment isrequired.	No information on dosing adjustment is available.
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

OVERDOSAGE

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 and exhibits a low potential for acute toxicity.

STORAGE/PRECAUTIONS

Store in a cool, dry and dark place between 15 - 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION

LEVOSCOT Tablets 250 & 500 mg are available in packing containing 10 tablets.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔
احتیاط: روشنی، نمی اور گرمی سے بچائیں۔
15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔
مستند ڈاکٹر کے نسخہ پر استعمال کریں۔

Complete Medical Information available only for doctors on request.

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