Halet

(Levofloxacin)

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۲۵۰ ملی گرام، ۵۰۰ ملی گرام

250mg & 500mg Tablets

FULL PRESCRIBING INFORMATION

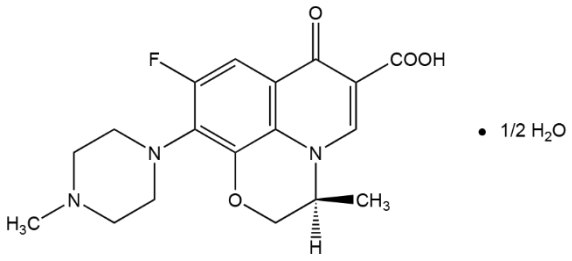
WARNING:

Fluoroquinolones, including HALET, 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 [*See Warnings and Precautions*].

1 DESCRIPTION

HALET is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name 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-carboxylicacid hemihydrate.

Figure 1: The Chemical Structure of Levofloxacin



The empirical formula is $C^{18}H^{20}FN^{3}O^{4}$ • ½ $H^{2}O$ and the molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble to freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered *freely soluble* in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: $Al^{+3}>Cu^{+2}>Zn^{+2}>Mg^{+2}>Ca^{+2}$.

Composition:
Halet Tablet 250mg:
Each film-coated tablet contains;
Levofloxacin …….. 250mg
(USP Specification)

Halet Tablet 500mg:
Each film-coated tablet contains;
Levofloxacin …….. 500mg
(USP Specification)

2 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of HALET and other antibacterial drugs, HALET 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.

HALET 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 in this section. HALET indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form).

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 *[see Clinical Pharmacology]*. Therapy with HALET may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

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

2.1 Nosocomial Pneumonia

HALET 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, combinationtherapy with an anti-pseudomonal β-lactam is recommended [see Clinical Studies.

2.2 Community-Acquired Pneumonia: 7-14 day Treatment Regimen

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

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

2.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

HALET 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 [see Dosage and Administration and Clinical Studies].*

2.4 Acute Bacterial Sinusitis: 5-day and 10-14 day Treatment Regimens HALET is indicated for the treatment of acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae,* or *Moraxella catarrhalis [see Clinical Studies (14.4)].*

2.5 Acute Bacterial Exacerbation of Chronic Bronchitis

HALET 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*.

2.6 Complicated Skin and Skin Structure Infections

HALET 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 [see Clinical Studies].*

2.7 Uncomplicated Skin and Skin Structure Infections

HALET 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*.

2.8 Chronic Bacterial Prostatitis

HALET is indicated for the treatment of chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or methicillin-susceptible *Staphylococcus epidermidis [see Clinical Studies].*

2.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen HALET is indicated for the treatment of complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis [see Clinical Studies].*

2.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen HALET 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 [see Clinical Studies]*.

2.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen

HALET is indicated for the treatment of acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia *[see Clinical Studies]*.

2.12 Uncomplicated Urinary Tract Infections

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

2.13 Inhalational Anthrax (Post-Exposure)

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

3 DOSAGE AND ADMINISTRATION

3.1 Dosage in Adult Patients with Normal Renal Function

The usual dose of HALET Tablets is 250 mg & 500 mg administered orally every 24 hours, as indicated by infection and described in Table 1. The usual dose of HALET is 250 mg or 500 mg administered by slow infusion over 60 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 [see Dosage and Administration.

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

Type of Infection[1]	Dosed Every 24 hours	Duration (days)[2]
Community Acquired Pneumonia[3]	500 mg	7-14
Acute Bacterial Sinusitis	500 mg	10-14
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Uncomplicated SSSI	500 mg	7-10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[6]	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3

1 Due to the designated pathogens [see Indications and Usage].
2 Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.
3 Due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug-resistant strains [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae [see Indications and Usage].
4 Due to Streptococcus pneumoniae (excluding multi-drug-resistant strains [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Indications and Usage].
5 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.
6 This regimen is indicated for cUTI due to Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa; and for AP due to E. coli.
7 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].
8 The safety of HALET 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 [see Warnings and Precautions, Use in Specific Populations, and Clinical Studies] Prolonged HALET therapy should only be used when the benefit outweighs the risk.

3.2 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

Type of Infection[1]	Dose	Freq. Once every	Duration[2]

Inhalational Anthrax (post-exposure)[3, 4] Pediatric patients > 50 kg and ≥ 6 months of age	500 mg	24 hr	60 days[4]
Pediatric patients < 50 kg and ≥ 6 months of age	8 mg/kg (not to exceed 250 mg per dose)	12 hr	60 days[4]

1 Due to *Bacillus anthracis [see Indications and Usage]*

2 Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

3 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]*

4 The safety of HALET in pediatric patients for durations of therapy beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients *[see Warnings and Precautions, Use in Specific Populations, and Clinical Studies]*. Prolonged HALET therapy should only be used when the benefit outweighs the risk.

3.3 Dosage Adjustment in Adults with Renal Impairment

Administer HALET with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced.

No adjustment is necessary for patients with a creatinine clearance ≥ 50 mL/min.

In patients with impaired renal function (creatinine clearance <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance *[see Use in Specific Populations]*.

Table 3 shows how to adjust dose based on creatinine clearance.

Table 3: Dosage Adjustment in Adult Patients with Renal Impairment (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)
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

3.4 Drug Interaction With Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

HALET Tablets

HALET 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 *[see Drug Interactions and Patient Counseling Information]*.

3.5 Administration Instructions

Food and HALET Tablets

HALET Tablets can be administered without regard to food. It is recommended that

Hydration for Patients Receiving HALET Tablets Adequate hydration of patients receiving oral or intravenous HALET should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones *[see Adverse Reactions* and *Patient Counseling Information].*

5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

5 CONTRAINDICATIONS

HALET is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterial

6 WARNINGS AND PRECAUTIONS

6.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including HALET, 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. HALET 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. *[see Adverse Reactions; Patient Counseling Information]*.

6.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including HALET. 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, urticarial, itching, and other serious skin reactions. HALET 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, presser amines, and airway management, as clinically indicated *[see Adverse Reactions; Patient Counseling Information].*

6.3 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 HALET. 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.

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The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted *[see Adverse Reactions; Patient Counseling Information].*

6.4 Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with HALET. 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 *[see Warnings and Precautions]*. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. HALET should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Adverse Reactions; Patient Counseling Information].*

6.5 Central Nervous System Effects

Convulsions and toxic psychoses have been reported in patients receiving fluoroquinolones, including HALET. 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 HALET, the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, HALET 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.)

6.6 *Clostridium difficile*-Associated Diarrhea

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

6.7 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 HALET. HALET 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

6.8 Prolongation of the QT Interval

Some fluoroquinolones, including HALET, 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 postmarketing surveillance in patients receiving fluoroquinolones, including HALET. HALET 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

6.9 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

HALET 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 HALET

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 quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species

6.10 Blood Glucose Disturbances

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with HALET, 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 HALET, HALET should be discontinued and appropriate therapy should be initiated immediately

6.11 Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity 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/phototoxicity occurs.

6.12 Development of Drug Resistant Bacteria

Prescribing HALET 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

7 ADVERSE REACTIONS

7.1 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 [see Warnings and Precautions
- Hypersensitivity Reactions [see Warnings and Precautions
- Other Serious and Sometimes Fatal Reactions [see Warnings and Precautions
- Hepatotoxicity [see Warnings and Precautions
- Central Nervous System Effects [see Warnings and Precautions
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions
- Peripheral Neuropathy [see Warnings and Precautions

- Prolongation of the QT Interval [see Warnings and Precautions
- Musculoskeletal Disorders in Pediatric Patients [see Warnings and Precautions
- Blood Glucose Disturbances [see Warnings and Precautions
- Photosensitivity/Phototoxicity [see Warnings and Precautions
- Development of Drug Resistant Bacteria [see Warnings and Precautions

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

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

7.2 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 HALET in 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 HALET for a wide variety of infectious diseases *[see Indications and Usage (1)]*. Patients received HALET 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 HALET doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of HALET 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 HALET-treated patients and less common adverse reactions, occurring in 0.1 to <1% of HALET-treated patients, are shown in
Table 6 and Table 7, respectively. The most common adverse drug reactions (≥3%) are
nausea, headache, diarrhea, insomnia, constipation, and dizziness.

8 DRUG INTERACTIONS

8.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

HALET Tablets

While the chelation by divalent cations is less marked than with other fluoroquinolones, concurrent administration of HALET 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 HALET administration.

8.2 Warfarin

No significant effect of HALET 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 postmarketing experience in patients that HALET enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and HALET use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if HALET is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding

8.3 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

8.4 Non-Steroidal Anti-Inflammatory Drugs

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

8.5 Theophylline

No significant effect of HALET 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 HALET is co•

administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels *[see Warnings and Precautions (5.5)].*

8.6 Cyclosporine

No significant effect of HALET 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 C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ 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 HALET or cyclosporine when administered concomitantly.

9 USE IN SPECIFIC POPULATIONS

9.1 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. HALET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

9.2 Nursing Mothers

Based on data on other fluoroquinolones and very limited data on HALET, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from HALET 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.

9.3 Pediatric Use

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

Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been studied. The pharmacokinetics of levofloxacin following a single intravenous dose were investigated in pediatric patients ranging in age from six 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.

Adverse Events

9.4 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as HALET. 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 HALET to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue HALET 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 HALET-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 HALET. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. HALET should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Warnings and Precautions].*

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using HALET 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 hypokalemia) *[see Warnings and Precautions].*

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 *[see Clinical Pharmacology]*.

9.5 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 HALET are not required following hemodialysis or CAPD *[see Dosage and Administration)].*

9.6 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.

10 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.

HALET exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of HALET: 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.

12.5 How to Supplied:

HALET 250: A carton containing Alu Alu blister strip of 10 tablets.
HALET 500: A carton containing Alu Alu blister strip of 10 tablets.

12.6 Storage Conditions/ Instruction:

Store at 25°C.
Protect form sunlight and moisture
Keep out of reach of children.

ہیلیٹ ٹیبلیٹس

۲۵۰ ملی گرام اور ۵۰۰ ملی گرام

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۲۵ ڈگری پر محفوظ کریں۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کی جائے۔

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