When used in empiric regimens for the treatment of CAP or for treatment of CAP caused by *Pseudomonas aeruginosa*, the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) recommend that levofloxacin be given in a dosage of 750 mg once daily. IDSA and ATS state that CAP should be treated for a minimum of 5 days and patients should be afebrile for 48–72 hours before discontinuing anti-infective therapy.

Nosocomial Pneumonia: 750mg once every 24 hours for 7–14 days.
Urinary Tract Infections and Prostatitis: 250mg once every 24 hours for 3 days.
For the treatment of complicated urinary tract infections or acute pyelonephritis, the usual adult dosage of levofloxacinis 250mg once every 24 hours for 10 days. Alternatively, adults can receive 750mg once every 24 hours for 5 days for the treatment of complicated urinary tract infections caused by *E. coli, K. pneumoniae,* or *P. mirabilis* or for the treatment of acute pyelonephritis caused by *E. coli.*
Chronic prostatitis: 500mg once every 24 hours for 28 days.

Anthrax
If oral levofloxacin is used for postexposure prophylaxis following suspected or confirmed exposure to aerosolized anthrax spores (inhalational anthrax), the usual adult dosage is 500mg once daily and the usual dosage in children 6 months of age or older is 500mg once daily in those weighing more than 50kg and 8mg/kg (not to exceed 250mg per dose) every 12 hours in those weighing less than 50kg. This same dosage is recommended if oral levofloxacin is used as an alternative for the treatment of anthrax when a parenteral regimen is not available† (e.g., when there are supply or logistic problems because large numbers of individuals require treatment in a mass casualty setting). (see Uses: Anthrax)
Chlamydial Infections: 500mg once daily for 7 days.

Gonorrhea and Associated Infections
Uncomplicated or Disseminated Gonorrhea, of uncomplicated cervical, urethral, or rectal gonorrhea caused by susceptible *Neisseria gonorrhoeae,* a single 250mg dose of oral levofloxacin has been used in adults and adolescents. Epididymitis caused by sexually transmitted enteric bacteria (e.g., *Escherichia coli*) or when culture or nucleic acid amplification tests are negative for *N. gonorrhoeae,* a dosage of 500mg of levofloxacin once daily for 10 days has been recommended by the CDC and others. Levofloxacin should not be used for treatment of epididymitis if *N. gonorrhoeae* may be involved. Mycobacterial Infections Levofloxacin must be used in conjunction with other antituberculosis agents.
Nongonococcal Urethritis 500mg once daily for 7 days. Pelvic Inflammatory Disease the drug should be given in a dosage of 500mg once daily for 14 days with or without oral metronidazole (500mg twice daily for 14 days). Levofloxacin should only be used for treatment of PID when cephalosporins are not feasible, irmed.
Travelers' Diarrhea: 500mg of oral levofloxacin once daily for 1–3 days.

• Dosage in Renal and Hepatic Impairment
Dosage of levofloxacin should be modified according to the degree of renal impairment in adults with creatinine clearances less than 50mL/minute. When used for the treatment of urinary tract infections in adults, levofloxacin dosage does not need to be modified when used for uncomplicated urinary tract infections in those with creatinine clearances of 10–49 mL/minute or complicated urinary tract infections or acute pyelonephritis in those with creatinine clearances of 20mL/minute or greater.

There are no dosage recommendations for pediatric patients with renal insufficiency.

Usual Dosage for Normal Renal Function (Clcr ≥ 50 mL/min)	Clcr (mL/min)	Dosage for Renal Impairment
250mg	20-49	Dosage adjustment not required
250mg	10-19	Uncomplicated UTIs: Dosage adjustment not required Other infections: 250mg every 48 hours
250mg	Hemodialysis or CAPD Patients	Information not available
500mg	20-49	Initial 500mg dose, then 250mg once every 24 hours
500mg	10-19	Initial 500mg dose, then 250mg once every 48 hours
500mg	Hemodialysis or CAPD Patients	Initial 500mg dose, then 250mg once every 48 hours; supplemental doses not required after dialysis
750mg	20-49	Initial 750mg dose, then 750mg once every 48 hours
750mg	10-19	Initial 750mg dose, then 500mg once every 48 hours
750mg	Hemodialysis or CAPD Patients	Initial 750mg dose, then 500mg once every 48 hours; supplemental doses not required after dialysis

Additional supplemental doses of levofloxacin are not necessary after dialysis or CAPD procedures. Adjustment of levofloxacin dosage in patients with hepatic insufficiency would not be expected to be necessary because most of the drug is excreted unchanged in urine.

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.

Availability:
500 mg tablet: Blisters Pack x 10's (Box of 30's)

Registration Number: DR - XY36092
Date of First Authorization: July 1, 2009
Revision Date: January 2019

STORE AT ROOM TEMPERATURES NOT EXCEEDING 30°C

Manufactured by
Lloyd Laboratories, Inc.
No. 10, Lloyd Ave,
First Bulacan Industrial City,
City of Malolos, Bulacan
for Natrapharm, Inc.
The Patriot Building
Km. 18, West Service Road,
SLEX, Sucat, Parañaque City

NTLVT500600IN1901

Natrapharm

Levofloxacin

Levofloxin-Natrapharm®

500mg Film-coated tablet
Antibacterial

Formulation:
Each film-coated tablet contains:
Levofloxacin..... 500mg

Indications:
Levofloxacin is the S-(–)-isomer of the fluoroquinolone antibacterial ofloxacin.
It is indicated for the:
- Treatment of respiratory tract infections
  - Acute bacterial exacerbations of chronic bronchitis susceptible to *Staphylococcus aureus* (oxacillin-susceptible [methicillin-susceptible] strains), *S. pneumoniae, H. influenzae, H. arainfluenzae,* or *M. catarrhalis*),
  - Acute bacterial sinusitis (*Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis*),
  - Community-acquired pneumonia, susceptible *S. aureus* (oxacillin-susceptible strains), S. pneumoniae (including penicillin-resistant strains [penicillin MIC of 2mcg/mL or greater]), *H. influenzae, H. parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, M. catarrhalis, Chlamydophila pneumoniae* (formerly *Chlamydia pneumoniae*), or *Mycoplasma pneumoniae.*
  - Nosocomial pneumonia *S. aureus* (oxacillin-susceptible strains), *S. pneumoniae, H. influenzae, Escherichia coli, K. pneumoniae, Ps. aeruginosa,* or *Serratia marcescens*). If the infection is known or suspected of being caused by *Ps. aeruginosa*, concomitant therapy with an antipseudomonal β-lactam anti-infective is recommended.
- Uncomplicated or complicated skin and skin structure infections caused by susceptible S. aureus (oxacillin-susceptible strains), *Enterococcus faecalis, S. yogenes,* or *Proteus mirabilis.*
- The treatment of mild to moderate uncomplicated urinary tract infections (UTIs) caused by susceptible *E. coli, K. pneumoniae,* or *S. saprophyticus.*
- The treatment of mild to moderate complicated UTIs caused by susceptible *E. faecalis, Enterobacter cloacae, E. coli, K. pneumoniae, P. mirabilis,* or *Ps. aeruginosa* and acute pyelonephritis caused by susceptible *E. coli,* including cases with concurrent bacteremia.
- The treatment of chronic prostatitis caused by susceptible *E. coli, E. faecalis,* or *S. epidermidis* (oxacillin-susceptible strains).
- Levofloxacin is used as an alternative for treatment of native or prosthetic valve endocarditis caused by fastidious gram-negative bacilli known as the HACEK group (*Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Haemophilus aphrophilus, H. influenzae, H. parainfluenzae, H. paraphrophilus, Kingella denitrificans, K. kingae*).
- The treatment of uncomplicated gonorrhea caused by susceptible *Neisseria gonorrhoeae.*
- The treatment of epididymitis most likely caused by sexually transmitted enteric bacteria (e.g., *E. coli*) or when culture or nucleic acid amplification tests are negative for *N. gonorrhoeae.*
- The treatment of meningitis caused by susceptible organisms (e.g., *Rhodococcus equi*).

Pharmacodynamics
Levofloxacin is generally considered to be about twice as active as ofloxacin, the racemic substance. Levofloxacin has a broad spectrum of activity which includes Gram-positive bacteria.

Pharmacokinetics
Levofloxacin is rapidly and almost completely absorbed after oral doses with peak plasma concentrations occurring within 1 to 2 hours. It is widely distributed into body tissues including the bronchial mucosa and lungs, but penetration into CSF is relatively poor.
Levofloxacin is about 30 to 40% bound to plasma proteins. Only small amounts are metabolised, to inactive metabolites. The elimination half-life of levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted largely unchanged, primarily in the urine with less than 5% as metabolites. It is not removed by haemodialysis or peritoneal dialysis.

Adverse Effects and Precautions
Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, levofloxacin should be stopped.

Contraindications
Known hypersensitivity to levofloxacin or other quinolones.

Warnings/Precautions

Aortic aneurysm and dissection
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physican in an emergency department.

Warnings
Tendinopathy and Tendon Rupture
Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all age groups. This risk is further increased in older adults (usually those over 60 years of age), individuals receiving concomitant corticosteroids, and kidney, heart, or lung transplant recipients. Other factors that may independently increase 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 receiving fluoroquinolones who did not have any of these risk factors.
Fluoroquinolone-associated tendinitis and tendon rupture most frequently involve the Achilles tendon and may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (shoulder), hand, biceps, thumb, and other tendon sites also reported.
Tendon rupture can occur during or following fluoroquinolone therapy and has been reported up to several months after completion of therapy. Advise patients to rest and refrain from exercise and contact a clinician at the first sign of tendinitis or tendon rupture (e.g., pain, swelling, or inflammation of a tendon or weakness

or inability to use a joint). (See Advice to Patients.) Discontinue levofloxacin if pain, swelling, inflammation, or rupture of a tendon occurs.

Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions reported in patients receiving fluoroquinolones, including levofloxacin. These reactions may occur with first dose. Some hypersensitivity reactions have been accompanied by cardiovascular collapse, hypotension or shock, seizures, loss of consciousness, tingling, angioedema (e.g., edema or swelling of the tongue, larynx, throat, or face), airway obstruction (e.g., bronchospasm, shortness of breath, acute respiratory distress), urticaria, pruritus, and other severe skin reactions. In addition, other possible severe and potentially fatal reactions (may be hypersensitivity reactions or of unknown etiology) have been reported most frequently after multiple doses. These include fever, rash or other 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 effects.
Discontinue levofloxacin at first appearance of rash, jaundice, or any other sign of hypersensitivity.

Institute appropriate therapy as indicated (e.g., epinephrine, corticosteroids, and maintenance of an adequate airway and oxygen).

Other Warnings/Precautions

Hepatotoxicity
Severe hepatotoxicity, including acute hepatitis, has occurred and sometimes resulted in death. Most cases of severe hepatotoxicity occurred within 6–14 days of initiation of levofloxacin therapy and were not associated with hypersensitivity reactions. The majority of fatal cases of hepatotoxicity were in geriatric patients 65 years of age or older.
Levofloxacin should be discontinued in any patient who experiences loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin or eyes, light colored bowel movements, or dark colored urine.

CNS Effects
Seizures, toxic psychoses, and increased intracranial pressure and CNS stimulation, which may lead to tremor, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts, have been reported with fluoroquinolones, including levofloxacin. Such nervous system effects may occur following the first dose of the drug.
Use with caution in patients with known or suspected CNS disorders (e.g., severe cerebral arteriosclerosis, epilepsy) or other risk factors that predispose to seizures or lower the seizure threshold (e.g., certain drugs, renal impairment). If nervous system effects occur, discontinue levofloxacin and institute appropriate measures.

Peripheral Neuropathy
Sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias, and weakness reported with fluoroquinolones, including levofloxacin. To prevent development of an irreversible condition, discontinue levofloxacin if symptoms of neuropathy (e.g., pain, burning, tingling, numbness, weakness) or other alterations of sensation (e.g., light touch, pain, temperature, position sense, vibratory sensation) occur.

Superinfection/*Clostridium difficile*-associated Diarrhea and Colitis (CDAD)
Possible emergence and overgrowth of nonsusceptible bacteria or fungi. Institute appropriate therapy if superinfection occurs.

Prolongation of QT Interval
Prolonged QT interval leading to ventricular arrhythmias, including torsades de pointes, reported with some fluoroquinolones, including levofloxacin. Avoid use of levofloxacin in patients with a history of prolonged QT interval, in those with uncorrected electrolyte disorders (e.g., hypokalemia), and in those receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents. Risk may be increased in geriatric patients.

Musculoskeletal Disorders
An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality) has been reported in pediatric patients receiving levofloxacin. Use in pediatric patients only for prevention of inhalational anthrax (postexposure) in those 6 months of age or older.

Hypoglycemia or Hyperglycemia
Hypoglycemia or hyperglycemia reported with fluoroquinolones, including levofloxacin. Blood glucose disturbances usually have occurred in patients with diabetes receiving insulin or oral hypoglycemic agents. Carefully monitor blood glucose concentrations in diabetic patients. Discontinue levofloxacin and initiate appropriate therapy immediately if hypoglycemic reaction occurs.

Resistance in *Neisseria gonorrhoeae*
N. gonorrhoeae with decreased susceptibility to fluoroquinolones (quinolone-resistant *N. gonorrhoeae*; QRNG) has been reported with increasing frequency within the last several years.Recent US data indicate that QRNG has continued to increase among men who have sex with men and among heterosexual males and is now present in all regions of the country. CDC states that fluoroquinolones should not be used to treat proven or suspected gonorrhea, including infections acquired within the US or acquired while traveling abroad.

Specific Populations

Pregnancy
No adequate and well-controlled studies in pregnant women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Distributed into milk following oral or IV administration; discontinue nursing or the drug.

Geriatric Use
No substantial differences in safety and efficacy relative to younger adults, but increased sensitivity cannot be ruled out. Risk of severe tendon disorders, including tendon rupture, is increased in older adults (usually those older than 60 years of age). This risk is further increased in those receiving concomitant corticosteroids. Use caution in geriatric adults, especially those receiving concomitant corticosteroids.

Risk of fatal hepatotoxicity may be increased in geriatric patients.
Risk of prolonged QT interval leading to ventricular arrhythmias may be increased in geriatric patients, especially those receiving concurrent therapy with other drugs that can prolong QT interval (e.g., class IA or III antiarrhythmic agents) or with risk factors for torsades de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

Consider age-related decreases in renal function when selecting dosage

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

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

Drug Interactions

• Drugs That Prolong QT Interval
Potential pharmacologic interaction (additive effects on QT interval prolongation). Avoid concomitant use with class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents.

• Antacids
Potential pharmacokinetic interaction (decreased levofloxacin absorption). Administer levofloxacin at least 2 hours before or 2 hours after antacids containing magnesium or aluminum.
• Antiarrhythmic Agents
Potential pharmacologic interaction (additive effect on QT interval prolongation).
Levofloxacin should be avoided in those receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents. Pharmacokinetic interaction with procainamide (increased half-life and decreased clearance of procainamide).

• Antidepressants
Potential pharmacologic interaction with fluoxetine or imipramine (additive effect on QT interval prolongation).

• Antidiabetic Agents
Potential pharmacodynamic interaction (altered blood glucose concentrations and symptomatic hyperglycemia or hypoglycemia) in diabetic patients receiving concomitant levofloxacin and antidiabetic therapy (e.g., insulin, glyburide). Careful monitoring of blood glucose concentrations recommended; discontinue levofloxacin if a hypoglycemic reaction occurs.

• Cimetidine
Potential pharmacokinetic interaction (slightly increased levofloxacin AUC and half-life). Not considered clinically important; levofloxacin dosage adjustments are not recommended.

• Corticosteroids
Concomitant use of corticosteroids increases the risk of severe tendon disorders (e.g., tendinitis, tendon rupture), especially in geriatric patients older than 60 years of age.

• Cyclosporine and Tacrolimus
Possible pharmacokinetic interactions with cyclosporine or tacrolimus (increased AUC of the immunosuppressive agent). Manufacturer of levofloxacin states that dosage adjustments
are not required; some clinicians suggest that plasma concentrations of the immunosuppressive agent be monitored if used concomitantly with levofloxacin.

• Didanosine
Potential pharmacokinetic interaction (decreased levofloxacin absorption). Administer levofloxacin at least 2 hours before or 2 hours after buffered didanosine (pediatric oral solution admixed with antacid).

• Digoxin
Pharmacokinetic interaction unlikely; no clinically important effect on pharmacokinetics of digoxin or levofloxacin.

• Iron, Multivitamins, and Mineral Supplements
Potential pharmacokinetic interaction (decreased levofloxacin absorption). Administer levofloxacin at least 2 hours before or 2 hours after ferrous sulfate or dietary supplements containing zinc, calcium, magnesium, or iron.

• Nonsteroidal Anti-inflammatory Agents (NSAIAs)
Potential pharmacologic interaction (possible increased risk of CNS stimulation and seizures). Animal studies suggest risk may be less than that associated with some other fluoroquinolones and that risk varies depending on the specific NSAIA.

• Probenecid
Potential pharmacokinetic interaction (increased levofloxacin AUC and half-life). Not considered clinically important; dosage adjustments are not required.

• Sucralfate
Potential pharmacokinetic interaction (decreased levofloxacin absorption); no pharmacokinetic interaction if given 2 hours apart. Administer levofloxacin at least 2 hours before or 2 hours after sucralfate.

• Theophylline
Pharmacokinetic interaction unlikely. However, pharmacokinetic interaction (increased theophylline half-life and increased risk of theophylline-related adverse effects) occurs with some other quinolones. Closely monitor serum theophylline concentrations and adjust theophylline dosage accordingly; consider that adverse theophylline effects (e.g., seizures) may occur with or without elevated theophylline concentrations.

• Warfarin
Potential pharmacologic interaction (increased prothrombin time). Monitor prothrombin time or other suitable coagulation tests and monitor for bleeding.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Dosage and Administration
Levofloxacin tablets may be given without regard to meals, antacids containing magnesium or aluminum, sucralfate, metal cations such as iron or zinc, and buffered didanosine may interfere with oral absorption of levofloxacin resulting in subtherapeutic systemic concentrations of the quinolone. To minimize the possibility of an interaction, patients should be instructed not to ingest antacids containing magnesium or aluminum, sucralfate, metal cations such as iron or zinc (including multivitamin preparations containing zinc), or buffered didanosine (pediatric oral solution admixed with antacids) concomitantly with or within 2 hours of a levofloxacin oral dose.

Respiratory Tract Infections
Acute Sinusitis: 500 mg once every 24 hours for 10–14 days. Alternatively, a dosage of 750 mg once every 24 hours for 5 days can be used.
Acute Exacerbations of Chronic Bronchitis: 500 mg once every 24 hours for 7 days.
For the treatment of community-acquired pneumonia (CAP), the usual adult dosage of levofloxacin is 500mg once every 24 hours for 7–14 days. Alternatively, a dosage of 750 mg once every 24 hours for 5 days can be used for treatment of CAP caused by S. pneumoniae (penicillin-susceptible strains), *Haemophilus influenzae, H. parainfluenzae, Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*.