Levofloxacin Ophthalmic Solution 0.5% is a sterile topical ophthalmic solution. Levofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. Levofloxacin is the pure (–)-(S)-enantiomer of the racemic drug substance, ofloxacin. It is more soluble in water neutral pH than ofloxacin.

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**CLINICAL PHARMACOLOGY:**

**Pharmacokinetics:**
Levofloxacin concentration in plasma was measured in 15 healthy adult volunteers at various time points during a 15 day course of treatment with Levofloxacin Ophthalmic Solution. The mean levofloxacin concentration in plasma 1 hour postdose, ranged from 0.86 ng/mL on Day 1 to 2.05 ng/mL on Day 15. The highest maximum mean levofloxacin concentration of 2.5 ng/mL was measured on Day 4 following 2 days of dosing every 2 hours for a total of 8 doses per day. Maximum mean levofloxacin concentrations increased from 0.94 ng/mL on Day 1 to 2.15 ng/mL on Day 15, which is more than 1,000 times lower than those reported after standard oral doses of levofloxacin. Levofloxacin concentration in tears was measured in 30 healthy adult volunteers at various time points following instillation of a single drop of Levofloxacin Ophthalmic Solution. Mean levofloxacin concentrations in tears ranged from 3.49 to 221.1 µg/mL during the 60-minute period following the single dose. The mean tear concentrations measured 4 and 6 hours postdose were 17.0 and 6.6 µg/mL. The clinical significance of these concentrations is unknown.

**Microbiology:**
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 fluoroquinolones antimicrobials involves the inhibition of bacterial topoisomerases 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 and is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

**AEROBIC GRAM-POSITIVE MICROORGANISMS**

- Corynebacterium species
- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus (Groups C/F)
- Staphylococcus (Group G)
- Viridans group streptococci

**AEROBIC GRAM-NEGATIVE MICROORGANISMS**

- Acinetobacter baumannii
- Haemophilus influenzae
- Salmonella microsors

*Efficacy for this organism was studied in fewer than 10 infections. The following in vitro data are also available, but their clinical significance in ocular infections is unknown. The safety and effectiveness of levofloxacin in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials. These organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the in vitro systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections.*

Levofloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of 0.001 to 0.015 mg/L (1 to 15 µg/mL) against most (>90%) of the following ocular pathogens: *Efficacy for this organism was studied in fewer than 10 infections. The following in vitro data are also available, but their clinical significance in ocular infections is unknown. The safety and effectiveness of levofloxacin in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials. These organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the in vitro systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections.*

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**Aerobic gram-positive microorganisms**

- Enterococcus faecalis
- Staphylococcus epidermidis
- Streptococcus pyogenes
- Aerobic gram-negative microorganisms
- Acinetobacter baumannii
- Haemophila influenzae
- Legionella pneumophila
- Morganella morgani
- Proteus mirabilis
- Pseudomonas aeruginosa
- Staphylococcus epidermidis
- Strptococcus pneumoniae

**Clinical Studies:**
In randomized, double-masked, multicenter controlled clinical trial where patients were dosed for 5 days, Levofloxacin Ophthalmic Solution demonstrated clinical cures in 79% of patients treated for bacterial conjunctivitis on the final study visit.
Levofloxacin Ophthalmic Solution 0.5% Leaflet

**INDICATIONS AND USAGE**
Levofloxacin Ophthalmic Solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

**AEROBIC GRAM-POSITIVE MICROORGANISMS**
Corynebacterium species
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae

**AEROBIC GRAM-NEGATIVE MICROORGANISMS**
Acinetobacter baumannii
Neisseria influenzae
Serratia marcescens

**ERGICITY for this organism was studied in fewer than 10 infections.**

**CONTRAINDICATIONS**
Levofloxacin Ophthalmic Solution is contraindicated in patients with a history of hypersensitivity to levofloxacin, to other quinolones, or to any of the components of this medication.

**WARNINGS**

**NOT FOR INJECTION.** Levofloxacin Ophthalmic Solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients infected with systemic quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to levofloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

**PRECAUTIONS**

**General**
As with other anti-infective agents, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slitlamp biomicroscopy, and where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

**Information for Patients**
Avoid contaminating the applicator tip with material from the eye, fingers or other source. Systemic quinolones have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reactions.

**Drug Interactions**
Specific drug interaction studies have not been conducted with Levofloxacin Ophthalmic Solution. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfering with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**
In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily oral administration; the highest dose (100 mg/kg/day) was 875 times the highest recommended human ophthalmic dose.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (S. typhimurium and E. coli), CHO/GT-473 forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the in vivo mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration assay (CHL cell line) and in vitro sister chromatid exchange (CHL/JL cell line) assays. Levofloxacin caused no impairment of fertility or reproduction in rats at oral doses as high as 360 mg/kg/day, corresponding to 3,150 times the highest recommended human ophthalmic dose.

**Pregnancy: Teratogenic Effects. Pregnancy Category C**
Levofloxacin at oral doses of 810 mg/kg/day in rats, which corresponds to approximately 7,000 times the highest recommended human ophthalmic dose, caused decreased fetal body weight and increased fetal mortality. No teratogenic effect was observed when rabbits were dosed orally as high as 50 mg/kg/day, which corresponds to approximately 400 times the highest recommended human ophthalmic dose, although a decrease in fetal body weight was observed when rabbits were dosed intravenously at high doses. No teratogenic effect was observed when rabbits were dosed orally at 5 mg/kg/day, which corresponds to approximately 40 times the highest recommended human ophthalmic dose. No teratogenic effect was observed in rabbits dosed intravenously at high doses. No teratogenic effect was observed in rabbits dosed intravenously at high doses. No teratogenic effect was observed in rabbits dosed intravenously at high doses. No teratogenic effect was observed in rabbits dosed intravenously at high doses. No teratogenic effect was observed in rabbits dosed intravenously at high doses. No teratogenic effect was observed in rabbits dosed intravenously at high doses. No teratogenic effect was observed in rabbits dosed intravenously at high doses.

Levofloxacin can cross the placenta and is excreted in human milk. Caution should be exercised when Levofloxacin Ophthalmic Solution is administered to a nursing mother.

**Pediatric Use:**
Safety and effectiveness in infants below the age of one year have not been established. Oral administration of quinolones has been shown to cause arthropathy in immature animals. There is no evidence that the ophthalmic administration of levofloxacin has any effect on weight bearing joints.

**Geriatric Use:**
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

**ADVERSE REACTIONS**
The most frequently reported adverse events in the overall study populations were transient decreased vision, fever, foreign body sensation, headache, transient ocular burning, dyspnea, urticaria, and itching. These events occurred in approximately 1-3% of patients. Other reported reactions occurring in less than 1% of patients included allergic reactions, lid edema, ocular dryness and ocular itching.

**Dosage and Administration**

**Days 1 and 2:**
Instill one to two drops in the affected eye(s) every 2 hours while awake, up to 8 times per day.

**Days 3 through 7:**
Instill one to two drops in the affected eye(s) every 4 hours while awake, up to 4 times per day.

**HOW SUPPLIED**
Levofloxacin Ophthalmic Solution 0.5% is supplied in a natural, low density polyethylene bottle with a controlled dropper tip and a tan, high density polyethylene cap in the following size:
Bottles of 5 mL, NDC 16571-150-50
Store at 20-25°C (68-77°F)

Rx only

Manufactured In India for:
Nexus Pharmaceuticals Inc., Vernon Hills, IL 60061.
Distributed by:
Pax Pharmaceuticals, LLC, Buffalo Grove, IL 60089.