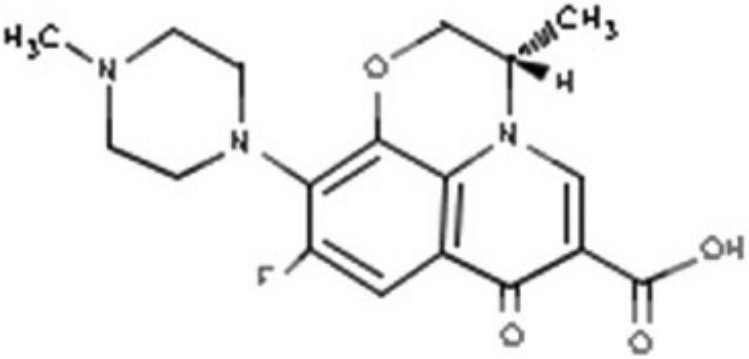
LEVOFLOXACIN- levofloxacin solution/ drops
Rising Pharmaceuticals, Inc.

Levofloxacin Ophthalmic Solution 0.5%
Sterile

DESCRIPTION:

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.

Structural formula:



Levofloxacin Hemihydrate

$C_{18}H_{20}FN_3O_4 \cdot ½\ H_2O$ Mol Wt. 370.38

Chemical Name:(-)-(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 (hemihydrate) is a yellowish-white crystalline powder. Each mL of Levofloxacin Ophthalmic Solution contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin.

Contains:
Active: Levofloxacin 0.5% (mg/mL); **Preservative:** benzalkonium chloride 0.005%;
Inactives: sodium chloride and water for injection. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH. Levofloxacin Ophthalmic Solution is isotonic and formulated at pH 6.5 with an osmolality of approximately 300 mOsm/kg. Levofloxacin is a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.

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 34.9 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 fluoroquinolone antimicrobials involves the inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoismerases), 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.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from β-lactam antibiotics and aminoglycosides, and therefore may be active against bacteria resistant to β-lactam antibiotics and aminoglycosides. Additionally, β-lactam antibiotics and aminoglycosides may be active against bacteria resistant to levofloxacin. Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Levofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

AEROBIC GRAM-POSITIVE MICROORGANISMS
Corynebacterium species*
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus (Groups C/F)
Streptococcus (Group G)
Viridans group streptococci

AEROBIC GRAM-NEGATIVE MICROORGANISMS
*Acinetobacter lwoffii**
Haemophilus influenzae
*Serratia marcescens**

*Efficacy for this organism was studied in fewer than 10 infections. The following *in vitro* data are also available, but their clinical significance in ophthalmic 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 2µg/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following ocular pathogens:

Aerobic gram-positive microorganisms
Enterococcus faecalis
Streptococcus agalactiae
Staphylococcus saprophyticus
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Acinetobacter anitratus
Legionella pneumophila
Acinetobacter baumannii

Moraxella catarrhalis
Citrobacter diversusi
Morganella morgqanii
Citrobacter freudii
Neisseria gonorrhoeae
Enterobacter aerogenes
Proteus mirabilis
Enterobacter agglomerans
Proteus vulgaris
Enteroacter cloacae
Providencia rettgeri
Escherichia coli
Providencia stuartii
Haemophilus arainfluenzae
Pseudomonas aeruginosa
Klebsiella oxytoca
Pseudomonas fluorescens
Klebsiella 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 day (day 6-10). Microbial outcome for the same clinical trials demonstrated an eradication rate for presumed pathogens of 90%.

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
Streptococcus (Groups C/F)
Streptococcus (Group G)
Viridans group streptococci

AEROBIC GRAM-NEGATIVE MICROORGANISMS
*Acinetobacter lwoffii**
Haemophilus influenzae
*Serratia marcescens**

*Efficacy 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 subconjunctially, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving 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-infectives, 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, interfere 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 dietary 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/HGPRT 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 (CHL cell line) and *in vitro* sister chromatid exchange (CHL/IU 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 maximum human ophthalmic dose, or when dosed intravenously as high as 25 mg/kg/day, corresponding to approximately 200 times the highest recommended human ophthalmic dose. There are, however, no adequate and well-controlled studies in pregnant woman. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin 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, ocular pain or discomfort, pharyngitis and photophobia. 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.

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharmaceuticals, Inc. at 1-866-562-4597 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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:
Rising Pharmaceuticals Inc.
Allendale, NJ 07401

Distributed by:
Pack Pharmaceuticals, LLC
Allendale, NJ 07401

———PRINCIPAL DISPLAY PANEL———

NDC 16571-150-50

PACK
Pharmaceuticals, LLC

LEVOFLOXACIN
OPHTHALMIC
SOLUTION
0.5%

FOR TOPICAL
APPLICATION
IN THE EYE

Rx only (5 mL) Sterile

LEVOFLOXACIN

levofloxacin solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16571-150

Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOFLOXACIN (UNII: 6GNT3Y5LMF) (LEVOFLOXACIN ANHYDROUS - UNII:RIX4E89Y14)	LEVOFLOXACIN ANHYDROUS	5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	0.05 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	9 mg in 1 mL
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16571-150-50	48 in 1 CASE	12/20/2010	
1		5 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077700	12/20/2010	

Labeler - Rising Pharmaceuticals, Inc. (835513529)

Establishment

Name	Address	ID/FEI	Business Operations
Indoco Remedies Ltd.		915851870	MANUFACTURE(16571-150)

Revised: 3/2017 Rising Pharmaceuticals, Inc.