HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use QUIXIN® ophthalmic solution safely and effectively. See full prescribing information for QUIXIN®.

QUIXIN® (levofloxacin ophthalmic solution) 0.5%
Sterile topical ophthalmic solution
Initial U.S. Approval: 1996

---------INDICATIONS AND USAGE----
QUIXIN® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Gram-positive bacteria:
Corynebacterium *species**
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumonia
Streptococcus (Groups C/F)
Streptococcus (Group G)
Viridans group streptococci*

Gram-negative bacteria:
*Acinetobacter lwoffii **
Haemophilus influenzae
*Serratia marcescens**

*Efficacy for this organism was studied in fewer than 10 infections (1)

---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. (2)

-----DOSAGE FORMS AND STRENGTHS-----
5 cc container filled with 5 mL sterile ophthalmic solution of levofloxacin, 0.5% (3)

---------CONTRAINDICATIONS--------
QUIXIN® solution is contraindicated in patients with a history of hypersensitivity to levofloxacin, to other quinolones, or to any of the components in this medication. (4)

--WARNINGS AND PRECAUTIONS--
- Hypersensitivity and anaphylaxis have been reported with systemic use of levofloxacin as well as topical use of other fluoroquinolones, including QUIXIN. (5.1)
- Prolonged use may result in the overgrowth of non-susceptible organisms, including fungi. (5.2)
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis. (5.3)

--------ADVERSE REACTIONS------
The most frequently reported adverse reactions in the overall study population were transient decreased vision, fever, foreign body sensation, headache, transient ocular burning, ocular pain or discomfort, pharyngitis and photophobia. These reactions 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. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Santen Incorporated at 1-415-268-9100 option #3 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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2 DOSAGE AND ADMINISTRATION

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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.

3 DOSAGE FORMS AND STRENGTHS

5 cc bottle filled with 5 mL sterile ophthalmic solution of levofloxacin, 0.5%.

4 CONTRAINDICATIONS

QUIXIN® solution is contraindicated in patients with a history of hypersensitivity to levofloxacin, to other quinolones, or to any of the components in this medication.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

In patients receiving systemically administered quinolones, including levofloxacin, 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 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.

5.2 Growth of Resistant Organisms with Prolonged Use

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 slit-lamp biomicroscopy, and where appropriate, fluorescein staining.

5.3 Avoidance of Contact Lens Wear

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

6 ADVERSE REACTIONS

The most frequently reported adverse reactions in the overall study population were transient decreased vision, fever, foreign body sensation, headache, transient ocular burning, ocular pain or discomfort, pharyngitis and photophobia. These reactions 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Teratogenic Effects: Levofloxacin at oral doses of 810 mg/kg/day in rats 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, at which systemic exposure was approximately 2,250 times that observed at the maximum recommended human ophthalmic dose, or when dosed intravenously as high as 25 mg/kg/day, at which systemic exposure was approximately 1000 times that observed at the maximum recommended human ophthalmic dose.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 QUIXIN® is administered to a nursing mother.

8.4 Pediatric Use

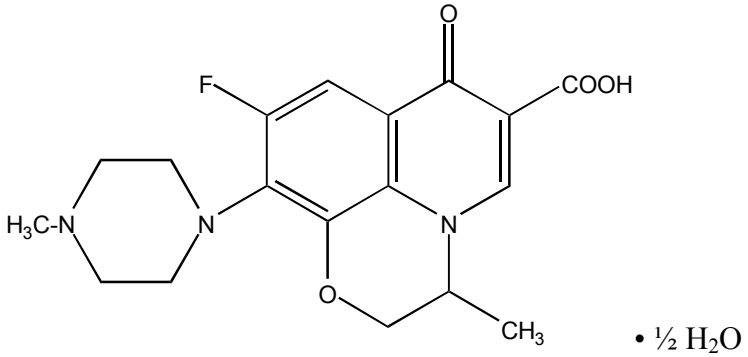
Safety and effectiveness in children below the age of six years have not been established. Oral administration of systemic quinolones has been shown to cause arthropathy in immature animals. There is no evidence that the ophthalmic administration of levofloxacin has any effect on weight bearing joints.

8.5 Geriatric Use

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

11 DESCRIPTION

QUIXIN® (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 a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure. Levofloxacin is the pure (-)-(S)-enantiomer of the racemic drug substance, ofloxacin. It is more soluble in water at neutral pH than ofloxacin.



$C_{18}H_{20}FN_3O_4$ •½ H2O Mol Wt 370.38

Chemical Name: (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4 benzoxazine-6-carboxylic acid hemihydrate.
Levofloxacin (hemihydrate) is a yellowish-white crystalline powder.

Each mL of QUIXIN® contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin.

Contains: Active: Levofloxacin 0.5% (5 mg/mL); **Preservative:** benzalkonium chloride 0.005%; **Inactives:** sodium chloride and water. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH to approximately 6.5.
UIXIN® solution is isotonic with an osmolality of approximately 300 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Levofloxacin is a member of the fluoroquinolone class of anti-infective drugs. *(See 12.4 Microbiology)*

12.3 Pharmacokinetics

Levofloxacin concentration in plasma was measured in 15 healthy adult volunteers at various time points during a 15-day course of treatment with QUIXIN® 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 2.25 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 QUIXIN® solution. Mean levofloxacin concentrations in tears ranged from 34.9 to 221.1 mcg/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 mcg/mL. The clinical significance of these concentrations is unknown.

12.3 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 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.

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 pneumonia
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 2 mcg/mL or less (systemic susceptible breakpoint) against most (≥90%) strains of the following ocular pathogens:

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

Aerobic gram-negative microorganisms:
Acinetobacter anitratus
Acinetobacter baumannii
Citrobacter koseri
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter cloacae
Escherichia coli
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumonia
Legionella pneumophila
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Pseudomonas fluorescens

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration for 2 years at doses up to 100

mg/kg/day, corresponding to plasma levels that were 1235 times the maximum clinical exposure, based on Cmax.

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, at which systemic exposure was estimated to be 23,000 times that at the maximum recommended human ophthalmic dose.

14 CLINICAL STUDIES

In randomized, double-masked, multicenter controlled clinical trials where patients were dosed for 5 days, QUIXIN® demonstrated clinical cures in 79% of patients treated for bacterial conjunctivitis on the final study visit day (day 6-10). Microbial outcomes for the same clinical trials demonstrated an eradication rate for presumed pathogens of 90%.

16 HOW SUPPLIED/STORAGE HANDLING

QUIXIN® (levofloxacin ophthalmic solution) 0.5% is supplied in a white, low density polyethylene bottle with a controlled dropper tip and a tan, high density polyethylene cap.

5mL fill in a 5cc container --- NDC 68669-135-05
Storage: Store at 15° – 25°C (59° – 77°F)

17. PATIENT COUNSELING INFORMATION

17.1 Avoid Contamination of the Product

Advise patients to avoid contaminating the applicator tip with material from the eye, finger, or other source.

17.2 Avoid Contact Lens Wear

Advise patients not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

17.3 Hypersensitivity Reactions

Systemically administered quinolones, including levofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Advise patients to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.

Manufactured by: Santen Oy, P.O. Box 33, FIN-33721 Tampere, Finland
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Daiichi Sankyo Co., Ltd., Tokyo, Japan