

QUIXIN®

(levofloxacin ophthalmic solution) 0.5%

BRIEF SUMMARY

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 the pure (-)-(-)-enantiomer of the racemic drug substance, ofloxacin. It is more soluble in water at neutral pH than ofloxacin.

QUIXIN® 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 (pyridoben-zoxazine) ring from positions 1 to 8 of the basic ring structure.

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%.

INDICATIONS AND USAGE

QUIXIN® 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

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.

WARNINGS

NOT FOR INJECTION.

QUIXIN® solution should not be injected subconjunctivally, 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 slit-lamp 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 reaction.

Drug Interactions: Specific drug interaction studies have not been conducted with QUIXIN®. 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 for 2 years; 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/IIU 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 women. 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 QUIXIN® 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 population 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.

Rx only

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U.S. PAT. NO. 5,053,407

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March 2004 Version

New Swimmer's Ear Guidelines Call for Use of Antimicrobial Drops, Pain Tx First

BY JOHN R. BELL

Associate Editor

The American Academy of Otolaryngology's first-ever guidelines for the diagnosis and treatment of acute otitis externa—commonly known as swimmer's ear—include a recommendation to treat pain and to use antimicrobial drops, rather than oral antibiotics, as first-line treatment.

The clinical practice guidelines were derived from a metaanalysis of nearly 3,000 published reports and were written by a panel of otolaryngologists from various subspecialties.

The document notes that starting treatment of acute otitis externa (AOE) with drops can help prevent bacterial resistance—even though many drops contain antibiotics themselves.

"It's a concentration issue," explained Dr. Richard Rosenfeld, who led the AAO guidelines writing committee. "You can

achieve a concentration with a topical drop that's about 1,000 times higher [at the infection site] than with a systemic drug. Topical [medication] is so incredibly potent that it overwhelms any ability of resistance. ... Dead bugs don't mutate—especially if you wipe them all out with a Scud missile of a drop."

But drops don't have to even contain antibiotics to be effective, he noted.

"We tested many types of topical therapy out there—antiseptics, various types of antibiotics, and also steroid-containing preparations. And they all seemed to have very comparable efficacy. We saw only minor, clinically irrelevant differences in efficacy.

"That doesn't mean that it's at all irrelevant what you use—for example, quinolone drops are perhaps most suitable for severe infections, because they're the most potent—but that's only anecdotal," added Dr. Rosenfeld, director of pediatric otolaryngology at Long Island College Hospital in New York.

As to prevention of swimmer's ear, Dr. Rosenfeld said that although there's no specific policy statement, in his opinion, the key is to avoid the things that trigger AOE.

Those include trauma or scratching of the ear canal and allowing excess water to build up in the ear canal and get trapped there. Trauma can be caused by cotton swabs or other objects inserted to remove wax or to scratch, or even by inserting foam ear plugs for swimming. Such earplugs are fine for preventing noise exposure because there is no water involved, he said. "But for swimming, just stuffing [foam] earplugs into your ears just does not work" and can lead to trauma, he said.

When water does get in the ear, Dr.

Rosenfeld recommended eliminating it with a hair dryer on a low setting.

Administering a few drops of isopropyl alcohol also works, and it is considerably less expensive than over-the-counter swimmer's ear drops.

Alternatively, a few drops of white vinegar and rubbing alcohol combined in a 50/50 ratio also can prevent swimmer's ear if applied after swimming or bathing. This combination is similar to some of the commercially available preparations. Vinegar is 5% acetic acid, and mixing it with the alcohol gets it down to 2.5% acetic acid. The alcohol helps kill bacteria and is a drying agent.

Drops don't cause systemic side effects, and you help keep down bacterial resistance.

DR. EAVEY

"It's a poor man's version of some of the rather expensive prescription drops. I wouldn't recommend it as a mainstay of treatment, but for people who are prone to AOE, it should help prevent it," he said.

"It's a lot simpler to use drops," commented Dr. Roland Eavey, professor of otology and laryngology at Harvard University, Boston.

"Drops don't cause systemic side effects, such as diarrhea—and by using drops, you help keep down bacterial resistance."

Dr. Eavey, who also is director of pediatric otolaryngology at Massachusetts Eye and Ear Infirmary in Boston, and who served on the AAO's guidelines panel for acute otitis media, agreed with the strong recommendation in favor of assessing and treating pain.

"Otitis externa can be very painful. On the assessment, when a child comes in with really bad external otitis externa, they first of all need pain relief," Dr. Eavey said.

He also shared the AAO's recommendation regarding differential diagnosis. "For example, although rare in childhood, malignant external otitis is a serious bone infection which mimics acute external otitis and can occur in insulin-dependent diabetics," he said.

He added his own specific recommendation: "You need to differentiate between a child with acute otitis and one with acute mastoiditis if there is swelling behind the ear. In that case, you need a clinical view of the eardrum and possibly a CT scan to make sure it's not mastoiditis.

But for garden-variety otitis externa, go



The outer ear of a patient with otitis externa is inflamed, and the inner ear is filled with crusted pus.

with the ear drops, and the patient should get better—if they're not much improved in 2-3 days, the patient should be reassessed.

Dr. Eavey also shared a treatment pearl. "My recommendation is also to have Mom or Dad warm up the drops in their hand or carry them in their pocket, because drops are often colder than the ear canal—and so to a child, it can feel like having ice water poured into their ear." He echoed a tip advocated in the guidelines that putting a wick in a severely swollen ear can help deliver the drops into the canal.

Dr. Seth Pransky, a pediatric otolaryngologist at Children's Hospital in San Diego, observed that although the guidelines are new, their advice is familiar to many physicians.

"Perhaps this might be considered new for primary care physicians, but the vast majority of otolaryngologists understand that this is a disease treated with topical rather than oral antibiotics," Dr. Pransky said.

"There are cases where orals are necessary, and the guidelines point that out—but they're a lot less common than garden variety, run-of-the-mill swimmer's ear, which is very painful."

Dr. Michael Pichichero, professor of microbiology and immunology at the University of Rochester (N.Y.) Medical Center, also approved of the recommendations. "I think the guidelines are very well written and comprehensive and appear to be evidence based—on as much evidence as we do have," he said in an interview.

In particular Dr. Pichichero noted that distinguishing between patients who have an intact eardrum and those who don't has a sizeable impact on the antibiotic choice—because if the eardrum is not intact, "we really should move to preference for the chloroquinolone antibiotic preparations, which are not ototoxic."

The document gave various treatment recommendations for specific AOE etiologies and advised against the use of alternative therapies such as ear candles. ■

The guidelines, which were published as a supplement to the journal *Otolaryngology-Head and Neck Surgery*, will be available free of charge at www.entnet.org.

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