

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

Manufactured by:
Santer Oy, P. O. Box 33, FIN-33721 Tampere, Finland

Licensed from:
Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan
U.S. PAT. NO. 5,053,407

Marketed by:
VISTAKON® Pharmaceuticals, LLC
Jacksonville, FL 32256 USA

VISTAKON PHARMACEUTICALS, LLC

March 2004 Version

LETTERS FROM MAINE

Pain by the Numbers

When the view from your living room includes hundreds of lobster trap buoys, out-of-town visitors expect to be served lobster for dinner. It often comes as an unnerving surprise to our guests, though, when they hear the clattering death throes of unfortunate crustaceans entering the steaming pot.

Inevitably, this terminal event shifts the conversation to the concept of who or what can feel pain. Marilyn and I try to reassure the squeamish that scientific research (probably funded by the state of Maine) has shown lobsters to lack the neurologic equipment to feel pain.

Pain has also become a hot topic in medicine, and "pain management" has joined the pantheon of medical buzzwords for the new millennium. The mantra at our hospitals seems to have become, "No pain shall go unmeasured or unmedicated." It has even crept out of the hospital. I have heard parents asking their toddlers, for whom counting is a recitation of 10 words they don't understand, to rate their pain on a scale from 1 to 10. This exercise in quantification is only slightly more futile than pointing to an array of pictograms with smiley and grumpy faces.

Sometimes, this well-intentioned passion to measure and eliminate pain can go awry and actually interrupt the timely discovery of the correct diagnosis. It may even interfere with a patient's ability to ac-

cess other forms of comfort, such as the soft words and gentle touch of a parent.

Now, don't get me wrong. I am not advocating that we return to the bad old days when pain was seriously undertreated because we physicians harbored an irrational fear of creating drug addicts. Most of us, myself included, still have a lot to learn about the pharmacologic management of pain, particularly in patients with terminal illnesses.

I think, however, that we should all look more closely at nonpharmacologic solutions and try harder to understand why some patients appear to experience more pain than others. There must be genetic and biochemical components to these differences in pain tolerance, but in the last few decades it has become obvious to me that uncertainty and depression are two critical factors in making pain less tolerable. Fortunately, these are things that I as a physician can influence with a combination of clinical skills and medications that are not usually considered analgesics.

A few years ago, for example, a urologist had to rescue me from my own inattention. At one point, he explained to me that, over the next 8 hours, I would be experiencing what could be very painful bladder spasms. He described their cause and assured me that they would be temporary. He encouraged me to ask for pain medication, but he also mentioned that it might temporarily slow my recovery.

Comforted by his confident and detailed explanation of what I was going to experience, I elected not to take any medication. He was correct about everything, including the severity of the pain, but because of its spasmodic nature and because I knew what to expect, it was tolerable. In effect, my skilled physician had used his own version of the Lamaze technique to help him manage my pain.

Ever since that experience I have tried whenever practical to tell a patient as much about his or her pain as I can: what is causing it, how long it will last, and what we can do to ameliorate it. Over the last few years, my efforts to dispel uncertainty seem to have made a positive difference for many of my patients. Ferreting out and treating the depression component have been more difficult tasks than educating and reassuring, particularly when the pain appears acutely and the patient is a child I don't know very well. However, by at least considering the role of depression in my patients' diminished pain tolerance, I can often get us started on the path toward the correct long-term solution.

Fortunately, for Marilyn and me, by the time the lobsters are ready to eat, the discussion has usually drifted away from pain management. Then it's time for a short course in crustacean anatomy and how to find the succulent meat hidden inside those crimson shells.

DR. WILKOFF practices general pediatrics in a multispecialty group practice in Brunswick, Maine. To respond to this column, write to Dr. Wilkoff at our editorial offices.

LETTERS

Answering the Call 24/7

For most of the 25 years since I came to this small community, I have been the only permanent fixture as far as pediatrics is concerned, and the only answering service we have is the hospital operator ("Answering Service vs. Machine," Efficient Pediatrician Practices, July 2005, p. 62).

Being solo means being on call 24/7 while in town. I let go of answering machines after I found myself listening to 50-60 messages. I give my home, office, and cell numbers to all my patients. I prefer that they call me directly.

I have never felt the need for an answering service. There is immense satisfaction on the part of parents when they can get hold of their own physicians.

It is a matter of personal choice. In the Western world, physicians do not want to be bothered during their off time. I came here from India with a clean slate, and the only orientation which made sense was unlimited and uncompromised availability to my patients.

I do not think I am going to change. The phone calls can be fun and challenging, and can provide a window into my patients' environment. There is a movement to put a price tag on this, but I am going to resist. Otherwise, there would be no difference between me and a lawyer. I always tell my patients they can call me back if they have

further concerns, or can go the hospital emergency department if necessary.

Amar Dave, M.D.
Ottawa, Ill.

Is RDA for Toddlers Too High?

Jennifer Orlet Fisher, Ph.D., is quoted as saying: "On average, a 2-year-old's intake is 1,249 calories, which is 32% higher than the estimated daily requirement" ("Promote Prevention to Parents With Chubby Toddlers," January 2006, p. 30). Several pediatrics texts cite the recommended dietary allowance of 100 cal/kg. An average female 2-year-old weighs 12 kg, and 1,249 calories would seem to be just about right.

Please invite the author to explain.

Stanley Gering, M.D.
Phoenix, Ariz.

Dr. Fisher replies:

The quote referred to a presentation of Dr. Barbara Devaney et al. in which the usual intake of food energy from a national random sample of 3,022 infants and toddlers was reported. Usual energy intakes were compared with estimated energy needs which were generated using the Institute of Medicine's estimated energy requirement (EER) equations, the current standard for estimating pediatric energy requirements to support the deposition of tissues consistent with good health. The usual energy

intake of toddlers between 12 and 24 months appeared to be approximately 32% higher than estimated energy needs.

Dr. Devaney comments:

The Institute of Medicine publishes the most up-to-date information on energy requirements of age and gender population subgroups (www.iom.edu/CMS/3788/4576/4340.aspx). In the IOM report, energy requirements are defined as the average energy intake that is needed to maintain energy balance in a healthy individual of a defined age, gender, weight, height, and level of physical activity. There is no RDA for energy because energy intakes above requirements would be expected to result in weight gain. According to the IOM report, the average weight for girls age 24 months is 12.1 kg, and the average EER is 997 kcal.

LETTERS

Letters in response to articles in PEDIATRIC NEWS and its supplements should include your name and address, affiliation, and conflicts of interest in regard to the topic discussed. Letters may be edited for space and clarity.

Mail: Letters, PEDIATRIC NEWS, 12230 Wilkins Ave., Rockville, MD 20852

Fax: 301-816-8738

E-mail: pdnews@elsevier.com