EyeKare

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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

GATIEYE HS™

GATIFLOXACIN EYE DROPS 0.5% W/V

COMPOSITION

Gatifloxacin equivalent to Gatifloxacin anhydrous 0.5% w/v, Benzalkonium Chloride Solution IP (as Preservative) 0.02% v/v, Water for Injections IP q.s.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS: Gatifloxacin ophthalmic solution 0.5% was administered to one eye of 6 healthy male subjects each in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days and finally 2 drops 8 times daily for 3 days At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/ml) in all subjects.

Microbiology: Gatifloxacin is an 8-methoxyfluoroquinolone with a 3- methyloiperazinyl substituent at C7. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial cell division. The mechanism of action of fluoroquinolones including gatifloxacin is different from that of aminoglycoside, macrolide, and tetracycline antibiotics. Therefore, gatifloxacin may be active against pathogens that are resistant to gatifloxacin. There is no cross-resistance between gatifloxacin and the aforementioned classes of antibiotics. Cross resistance has been observed between systemic gatifloxacin and some other fluoroquinolones. Resistance to gatifloxacin in vitro develops via multiple-step mutations. Resistance to gatifloxacin in vitro occurs at a general frequency of between $1x10^{-7}$ to $1x10^{-10}$. Gatifloxacin has been shown to be active against most strains of the following organisms both in vitro and clinically, in conjunctival infections as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-Positive: Comyebaterium propinquum* Staphylococcus aureus Staphylococcus epidermidis Streptococcus mitis* Streptococcus pneumoniae

Aerobes, Gram-Negative: Haemophilus influenzae. *Efficacy for this organism was studied in fewer than 10 infections. The following in vitro data are available, but there clinical significance in ophthalmic infections is unknown. The safety and effectiveness of Gatieye HS in treating ophthalmic infections due to the following organisms have not been established in adequate and well-controlled clinical trials. The following 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 following list of organisms is provided as guidance only in assessing the potential treatment of conjuctival infections. Gatifloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of 2ug/mL or less (systemic susceptible breakpoint against most > 90%) strains of the following ocular pathogens.

Aerobs, Gram-Positive: Listeria monocytogenes. Staphylococcus saprophyticus. Streptococcus agalactiae. Streptococcus pyrogen. Streptococcus viridans Group. Streptococcus Groups C, F, G.

Aerobes, Gram-negative: Acinetobacter iwoffii. Enterobacter aerogenes. Enterobater cloacae. Escherichia coli. Citrobacter frenundii. Citrobacter koseri.Haemophilus parainfluenzae. Klebsiella oxytoca. Klebsiella pneumoniae. Moraxella catarrhalis. Morganella morganii Neisseria gonorrhoeae. Neisseria meningitides. Proteus vulgaris. Serratia marcescens. Vibrio cholerae. Yersinia enterocolitica.

Other micro organisms: Chlamydia pneumoniae. Legionella pneumophila. Mycobacterium marinum. Mycobacterium fortuitum Mycoplasma pneumoniae.

Anaerobic Microorganisms: Bacteroides fragilis. Clostridium perfringens

Clinical Studies: In a randomized, double masked, multicenter clinical trial, where patients were dosed for 5 days, Gatieye HS solution was superior to its vehicle on day 5-7 in patients with conjunctivitis and positive conjunctival cultures. Clinical outcomes for the trial demonstrated clinical cure of 77% (40/52) for the gatifloxacin treated group versus 58% (28/48) for the placebo treated group. Microbiological outcomes for the same clinical trial demonstrated statistically superior eradication rate for causative pathogens of 92% (48/52) for gatifloxacin vs. 72% (34/48) for placebo. Please note that required microbiological eradication does not always correlate with clinical outcome in anti infective trials.

INDICATIONS AND USAGE : Gatieye HS solution is indicated for the treatment of external bacterial infections of the eye.

CONTRAINDICATIONS : Gatieye HS solution is contraindicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS : NOT FOR INJECTION

Gatieye HS solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye. in patients receiving systemic quinolones, including gatifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. 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 gatifloxacin 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 nonsusceptible organisms, including fungi. If superinfection occurs discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with 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, including gatifloxacin, 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 Gatieye HS 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: There was no increase in neoplasms among B6c3f1 mice given gatifloxacin in the diet for 18 months at doses averaging 81 mg/kg/day in males and 90mg/kg/day in females. These doses are approximately 2000-fold higher than the maximum recommended ophthalmic dose of 0.04 mg/kg/day in a 50 kg human.

There was no increase in neoplasms among Fischer 344 rats given gatifloxacin in the diet for 2 years at doses averaging 47mg/kg/day in males and 139 mg/kg/day in females (1000 and 3000-old higher, respectively, than the maximum recommended ophthalmic dose). A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of approximately 2000-fold higher than the maximum recommended ophthalmic dose. Fisher 344 rats have a high spontaneous background rate of LGL leukemia and the incidence in high-dose males only slightly exceeded the historical control range established for this strain. ingenetic toxicity tests, gatifloxacin was positive in 1 of 5 strains used in bacterial reverse mutations assays: Salmonella strain Ta102. Gatifloxacin was positive in vitro mammalian cell mutation and chromosome aberration assays. Gatifloxacin was positive in vitro unscheduled DNA synthesis in rat hepatocytes. Gatifloxacin was negative in vivo micronucleus tests in mice, cytogenetics tests in rats, and DNA repair test in rats. the findings may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase. There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 4500-fold higher than the maximum recomended ophthalmic dose for Gatieye).

Pregnancy: Teratogenic effects. Pregnancy Category C : There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day (approximately 1000- fold higher than the maximum recommended ophthalmic dose). However, skeletal/ craniofacial malformations or delayed ossification, atrial enlargement, and reduced foetus weight were observed in fetus from rats given ≥ 150mg/kg/day (approximately 3000-fold higher than the maximum recommended ophthalmic dose). In a prinatal/postnatal study, increased late post- implantation loss and neonatal/prinatal mortalities were observed at 200mg/kg/day (approximately 4500 times the maximum recommended ophthalmic dose). Because there are no adequate and well controlled studies in pregnant women, Gatieye HS solution should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers: Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when gatifloxacin is administered to a nursing woman.

Paediatric Use: Safety and effectiveness in infants below the age of one year have not been established.

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

ADVERSE REACTIONS

Ophthalmic Use: The most frequently reported adverse events in the overall study population were conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis. These events occured in approximately 5-10% of patients. Other reported reactions occuring in 1-4% of patients were chemosis, conjunctivial hemorrhage, dry eye, eye discharge, eye irritation, eye pain, eyelid endema, headache, red eye, reduced visual acuity and taste disturbance.

DOSAGE AND ADMINISTRATION : The recommended dosage regimen for the treatment of bacterial conjunctivities is: Days 1 and 2: Instill one drop every two hours in the affected eye (s) while awake, up to 8 times daily. Days 3 to 7: Instill one drop up to four times daily while awake.

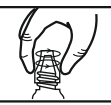
INCOMPATIBILITIES: None known.

PACKING : Gatieye HS Eye Drops are available in 5ml in ***Iyondellbasel Purell*** low density polyethylene dispensing system consisting of plastic bottle with good flexibility. Tamper evidence ring around the closure and neck area of the bottle.

STORAGE INSTRUCTIONS : Store in cool & dry place. Protect from light. Keep out of reach of children.

Use the solution within one month after opening the container.
Not for injection, For external use only

INSTRUCTIONS FOR USE

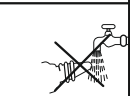


Rotate cap anticlockwise to break the seal.

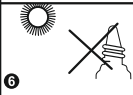
The vial is now ready for use; turn it up side down. Squeeze the walls of the vial gently to deliver sterile drop into the eye.

Replace the cap. Tighten it firmly and keep the vial closed for subsequent use.

Do not touch the nozzle.



Do not rinse the nozzle.



Do not expose to Sunlight.

State of the art technology from Eyekare Ltd.

Trade Mark applied for

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