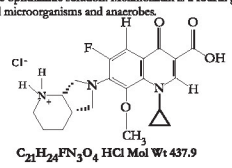
Fortymox

Moxifloxacin hydrochloride ophthalmic solution 0.5% as base

DESCRIPTION :

FORTYMOX (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile ophthalmic solution. Moxifloxacin is a fourth generation fluoroquinolone antibacterial agent active against a broad spectrum of Gram-positive and Gram-negative ocular pathogen, atypical microorganisms and anaerobes.



$C_{21}H_{24}FN_3O_4$ HCl Mol Wt 437.9

Chemical Name :

1-Cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3- quinolinecarboxylic acid, monohydrochloride. Moxifloxacin differs from other quinolones in that it has a methoxy function at the 8 position, and an S, S- configured diazabicyclononyl ring moiety at the 7-position.Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder

Composition :

Each ml of **FORTYMOX** solution contains :

Active : 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.; **preservative :** None. Product itself-preserved.

Inactives : Boric acid, sodium chloride, and water for injection. May also contain hydrochloric acid/sodium hydroxide to adjust pH.

FORTYMOX solution is an isotonic solution with an osmolality of approximately 290 mOsm/kg.

CLINICAL PHARMACOLOGY :

Pharmacokinetics/Pharmacodynamics :

Following topical ocular administration of **FORTYMOX**, moxifloxacin was absorbed to systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who received bilateral topical ocular doses of **FORTYMOX** solution 3 times a day for 4 days. The mean steady-state Cmax and AUC were 2.7ng/ml and 41.9 ng-hr/ml, respectively. These exposure values are approximately 1,600 and 1,200 times lower than the mean Cmax and AUC reported after well tolerated therapeutic 400 mg oral dose of moxifloxacin. The plasma half life of moxifloxacin was estimated to be 13 hours.

Microbiology :

Moxifloxacin has in vitro activity against wide range of gram-positive and gram-negative microorganisms. Moxifloxacin inhibits the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. The C8 methoxy moiety of moxifloxacin also lessens the selection of resistant mutants of gram positive bacteria compared to the C8-H moiety found in older fluoroquinolones. Moxifloxacin's bulky C7 substituent group interferes with the quinolone efflux pump mechanism of bacteria. Moxifloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentration. Fluoroquinolones, including moxifloxacin , differ in chemical structure and mode of action from beta lactams antibiotics, macrolides and aminoglycosides, and therefore may be active against bacterial resistant to beta lactam antibiotics, macrolide and aminoglycosides. Therefore, organisms resistant to these drugs may be susceptible to moxifloxacin. In vitro resistance to moxifloxacin develops slowly via multiple-step mutations and occurs at a general frequency of between 10^{-9} to 10^{-11} for Gram-positive bacteria. Moxifloxacin 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:

Gram-positive bacteria :

Corynebacterium species, *Microbacterium* species, *Micrococcus luteus*{including erythromycin, gentamycin, tetracycline, and/or trimethoprim resistant strains}, Mycobacterium species,
Staphylococcus aureus {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
Staphylococcus epidermidis {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
Staphylococcus haemolyticus {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
Staphylococcus hominis {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
Staphylococcus warneri {including erythromycin resistant strains}
Streptococcus mitis {including penicillin, erythromycin, tetracycline, and/or trimethoprim resistant strains}
Streptococcus pneumoniae {including penicillin, erythromycin, gentamycin, tetracycline, and/or trimethoprim resistant strains}
Streptococcus viridans group {including penicillin, erythromycin, tetracycline, and/or trimethoprim resistant strains}

Gram-negative bacteria :

Acinetobacter species, *Haemophilus aleonos* {including ampicillin resistant strains}
Haemophilus influenza {including ampicillin resistant strains }
Klebsiella pneumonia, Moraxella catarrhalis, Pseudomonas aeruginosa

Other microorganisms :

Chlamydia trachomatis
Moxifloxacin has been shown to be active in vitro against most strain of the following organisms; however, the clinical significance of these data is unknown

Gram-positive bacteria :

Arthrobacter species, *Bacillus cereus, bacillus thuringensis, Corynbacterium ascolens, Corynbacterium amycolatum, Corynbacterium bovis, Corynbacterium macginleyi, Corynbacterium propinqum, Corynbacterium pseudodiphtheriticum, Enterococcus faecalis, Exiguobacterium* species, *Kocuria kristinae, Kocuria kindae, Kocuria rhizophila, Listeria monocytogenes, Microbacterium barmaniae, Microbacterium oxididis, Rothsia mucilaginosus, Staphylococcus arlettae, Staphylococcus capitis, Staphylococcus caprae, Staphylococcus cohnii, Staphylococcus lugdunensis, Staphylococcus pasteuri, Staphylococcus saprophyticus, Staphylococcus sciuri, Streptococcus agalactiae, Streptococcus conjunctivus, Streptococcus cristatus, Streptococcus dysgalactiae, Streptococcus mitis, Streptococcus group C, D and F, Streptococcus ocularis, Streptococcus oralis, Streptococcus parasanguinis, Streptococcus pyogenes, Streptococcus salivarius, Streptococcus sanguis, Streptococcus schlechii*

Gram-negative bacteria :

Achromobacter xylosoxidans, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter johnsonii, Acinetobacter junii, Acinetobacter lwoffii, Acinetobacter mumbaia, Acinetobacter schindleri, acinetobacter ursingii, Aeromonas caviae, Chryseobacterium indologenes, Chryseobacterium species, Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter barmaechei, Escherichia coli, Klebsiella oxytoca, Moraxella atlaensis, Morganella morganii, Neisseria gonorrhoeae, Pantoea agglomerans, Proteus mirabilis, Proteus vulgaris, Pseudomonas oryzihabitans, Pseudomonas stutzeri, Serratia liquefaciens, Serratia marcescens, Stenotrophomonas maltophilia

Anaerobic microorganisms :

Clostridium perfringens, Fusobacterium species, *Prophyromonas* species, *Prevotella* species, *Propionobacterium acnes*

Other organisms :

Atypical *Mycobacterium, Chlamydia pneumonia, Legionella pneumophila, Mycobacterium avium, Mycobacterium marinum, Mycoplasma pneumonia.*

Clinical studies :

Moxifloxacin solution has been studied in patients from newborns to adults, including geriatric patients. In three randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, Moxifloxacin solution produced clinical cures in 80% to 94% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of base line pathogens ranged from 85% to 97%. In one of these trials in pediatric patients from birth to one month of age, Moxifloxacin solution produced clinical cure in 80% of patients of bacreial conjunctivitis, Microbiological success rates for the eradication of baseline pathogens was 92%. In a randomized, double-masked, multicenter, controlled clinical trial in which patients were dosed 2 times a day for 3 days, Moxifloxacin solution produced clinical cure in 74% of patients treated for bacterial conjunctivitis. Microbiological success rate for the eradication of the baseline pathogens was 81%.

Special populations :

The pharmacokinetic parameters of oral moxifloxacin are not significantly altered by mild, moderate, or severe renal impairment. No dosage adjustment of **FORTYMOX** solution is necessary in patients with renal impairment. The pharmacokinetic parameters of oral moxifloxacin were not significantly altered in patients with mild to moderate hepatic insufficiency (child pugh class A and B). Studies were not performed in patients with severe hepatic impairment (child pugh class C). Because of low systemic exposure by the topical route of the administration, no dosage adjustment of Moxifloxacin solution is needed in patients with hepatic impairment.

INDICATIONS AND USAGE :

FORTYMOX solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Gram-positive bacteria :

Corynebacterium species, *Microbacterium* species, *Micrococcus luteus*{including erythromycin, gentamycin, tetracycline, and/or trimethoprim resistant strains}, *Staphylococcus aureus* {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
Staphylococcus epidermidis {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
Staphylococcus haemolyticus {including methicillin, erythromycin, gentamycin, ofloxacin, tetracycline, and/or trimethoprim resistant strains}
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Streptococcus pneumonia {including penicillin, erythromycin, tetracycline, and/or trimethoprim resistant strains}
Streptococcus viridans group {including penicillin, erythromycin, tetracycline, and/or trimethoprim resistant strains}

Gram-negative bacteria :

Acinetobacter species, *Haemophilus aleonae* {including ampicillin resistant strains}
Haemophilus influenza {including ampicillin resistant strains }
Klebsiella pneumonia, Moraxella catarrhalis, Pseudomonas aeruginosa

Other micro-organisms :

Chlamydia trachomatis.
Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS :

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

WARNINGS :

In patients receiving systemically administered quinolones, including moxifloxacin, 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 moxifloxacin occurs, discontinue use of 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.

PATIENT INFORMATION :

Avoid contaminating the applicator tip with material from the eye, fingers or other source.
Systemically administered quinolones including moxifloxacin 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 :

While Drug-drug interaction studies have not been conducted with Moxifloxacin solution, they have been conducted with the oral product at much higher systemic exposures than are achieved by topical ocular route. Unlike some other fluoroquinolones, no clinically significant drug-drug interaction between systemically administered moxifloxacin and itraconazole, theophylline, warferin, digoxin, oral contraceptives, probinicid, ranitidine or glyburide have been observed. In vitro studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility :

Moxifloxacin was not mutagenic in four bacterial strains used in the Ames Salmonella reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity in vivo in a micronucleus test or a dominant lethal test in mice. Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day.

Pregnancy: Teratogenic Effects :

Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. Since there are no adequate and well-controlled studies in pregnant women, **FORTYMOX** solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers : Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when **FORTYMOX** solution is administered to a nursing mother.

Pediatric Use : FORTYMOX solution has been shown to be safe and effective in pediatric patients including neonates. There is no evidence that the ophthalmic administration of **FORTYMOX** solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

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

ADVERSE REACTIONS :

No serious ophthalmic or systemic adverse reactions related to FORTYMOX solution were reported. Adverse reactions were generally mild and occurred at an incidence similar to placebo (vehicle). The most frequently reported event was transient ocular discomfort (blurring/stinging) reported at an incidence of 2.9%. Other reported events included headache, keratitis, ocular pain, ocular pruritus, ocular hyperemia, pharyngitis and subconjunctival hemorrhage which were reported at an incidence of 0.5% to 1%.

Postmarketing Experience: Exacerbation of myasthenia gravis.

Dose :

Instill 1 drop in the infected eye 3 times a day for 4 days

Pack:

Carton box containing white plastic (LDPE) 10 ml / 5 ml bottle with dropper, white plastic cover & insert leaflet.

Storage:

Store at temperature not exceeding 30°C.
Don't use longer than 1 month after first opening.
Medical prescription only

Manufactured by
Orchidia Pharmaceutical Industries
Industrial Zone - Al-Obour City, Egypt

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Orchidia Pharmaceutical Ind.
www.orchidiapharma.com