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

MOXIF

1. Generic Name

Moxifloxacin Eye Drops I.P.

2. Qualitative and quantitative Composition:

Moxifloxacin Hydrochloride I.P.

Eq. to Moxifloxacin …… 0.5% w/v

Preservative:

Benzalkonium Chloride

Solution I.P. …… 0.02% w/v

Aqueous Buffered Vehicle ……. q.s.

For Ophthalmic use

The List of Excipients used are Sodium Chloride, Borax, Boric Acid, Benzalkonium Chloride Solution and Hydroxy Propyl Methyl Cellulose.

3. Dosage form and strength

Dosage form: Drops

Strength: 0.5% w/v

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for Bacterial Conjunctivitis.

4.2. Posology and method of administration

Posology

Instil one drop in the affected eye 3 times a day for 7 days.

Method of administration

Moxifloxacin ophthalmic solution is for topical ophthalmic use.

4.3. Contraindications

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

4.4. Special warnings and precautions for use

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycaemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are:

- Disturbances in attention
- Disorientation
- Agitation

- Nervousness
- Memory impairment
- Serious disturbances in mental abilities called delirium

Hypersensitivity Reactions

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.

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 bio microscopy, and, where appropriate, fluorescein staining.

Avoidance of Contact Lens Wear

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

4.5. Drugs interactions

Drug-drug interaction studies have not been conducted with moxifloxacin ophthalmic solution. 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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with moxifloxacin ophthalmic solution in pregnant women to inform any drug-associated risks.

Oral administration of moxifloxacin to pregnant rats and monkeys and intravenously to pregnant rabbits during the period of organogenesis did not produce adverse maternal or fetal effects at clinically relevant doses. Oral administration of moxifloxacin to pregnant rats during late gestation through lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant doses.

Data

Animal Data

Embryo-fetal studies were conducted in pregnant rats administered with 20, 100, or 500 mg/kg/day moxifloxacin by oral gavage on Gestation Days 6 to 17, to target the period of organogenesis. Decreased fetal body weight and delayed skeletal development were observed at 500 mg/kg/day [277 times the human area under the curve (AUC) at the recommended human ophthalmic dose]. The No-Observed-Adverse-Effect-Level (NOAEL) for

developmental toxicity was 100 mg/kg/day (30 times the human AUC at the recommended human ophthalmic dose).

Embryo-fetal studies were conducted in pregnant rabbits administered with 2, 6.5, or 20 mg/kg/day moxifloxacin by intravenous administration on Gestation Days 6 to 20, to target the period of organogenesis. Abortions, increased incidence of fetal malformations, delayed fetal skeletal ossification, and reduced placental and fetal body weights were observed at 20 mg/kg/day (1086 times the human AUC at the recommended human ophthalmic dose), a dose that produced maternal body weight loss and death. The NOAEL for developmental toxicity was 6.5 mg/kg/day (246 times the human AUC at the recommended human ophthalmic dose).

Pregnant cynomolgus monkeys were administered moxifloxacin at doses of 10, 30, or 100 mg/kg/day by intragastric intubation between Gestation Days 20 and 50, targeting the period of organogenesis. At the maternal toxic doses of ≥ 30 mg/kg/day, increased abortion, vomiting, and diarrhea were observed. Smaller fetuses/reduced fetal body weights were observed at 100 mg/kg/day (2864 times the human AUC at the recommended human ophthalmic dose). The NOAEL for fetal toxicity was 10 mg/kg/day (174 times the human AUC at the recommended human ophthalmic dose).

In a pre- and postnatal study, rats were administered moxifloxacin by oral gavage at doses of 20, 100, and 500 mg/kg/day from Gestation Day 6 until the end of lactation. Maternal death occurred during gestation at 500 mg/kg/day. Slight increases in the duration of pregnancy, reduced pup birth weight, and decreased prenatal and neonatal survival were observed at 500 mg/kg/day (estimated 277 times the human AUC at the recommended human ophthalmic dose). The NOAEL for pre- and postnatal development was 100 mg/kg/day (estimated 30 times the human AUC at the recommended human ophthalmic dose).

Lactation

Risk Summary

There is no data regarding the presence of moxifloxacin ophthalmic solution in human milk, the effects on the breastfed infants, or the effects on milk production/excretion to inform risk of moxifloxacin ophthalmic solution to an infant during lactation.

A study in lactating rats has shown transfer of moxifloxacin into milk following oral administration.

Systemic levels of moxifloxacin following topical ocular administration are low, and it is not known whether measurable levels of moxifloxacin would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for moxifloxacin ophthalmic solution and any potential adverse effects on the breastfed child from moxifloxacin ophthalmic solution.

Pediatric Use

The safety and effectiveness of moxifloxacin ophthalmic solution have been established in all ages. Use of moxifloxacin ophthalmic solution is supported by evidence from adequate and well controlled studies of moxifloxacin ophthalmic solution in adults, children, and neonates.

There is no evidence that the ophthalmic administration of moxifloxacin ophthalmic 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.

4.7. Effects on ability to drive and use machines

Moxifloxacin ophthalmic solution has no or negligible influence on the ability to drive and use machines. However, as with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery.

4.8. Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1%-6% of patients. Non ocular adverse events reported at a rate of 1%-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of the medicinal product. The total amount of moxifloxacin in a single container is too small to induce adverse effects after accidental ingestion.

5. Pharmacological properties

5.1. Mechanism of Action

Moxifloxacin is a member of the fluoroquinolone class of anti-infective drugs. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, aminoglycosides, or tetracyclines. Therefore, moxifloxacin may be active against pathogens that are resistant to these antibiotics, and these antibiotics may be active against pathogens that are resistant to moxifloxacin. There is no cross-resistance between moxifloxacin and the aforementioned classes of antibiotics. Cross-resistance has been observed between systemic moxifloxacin and some other quinolones.

5.2. Pharmacodynamic properties

The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

In vitro resistance to moxifloxacin develops via multiple-step mutations. Resistance to moxifloxacin occurs in vitro at a general frequency of between 1.8×10^{-9} to less than 1×10^{-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.

Aerobic Gram-Positive Microorganisms

Corynebacterium species*

Micrococcus luteus*

Staphylococcus aureus

Staphylococcus epidermidis

Staphylococcus haemolyticus

Staphylococcus hominis

Staphylococcus warneri*

Streptococcus pneumoniae

Streptococcus viridans group

Aerobic Gram-Negative Microorganisms

Acinetobacter lwoffi*

Haemophilus influenza

Haemophilus parainfluenzae*

Other Microorganisms

Chlamydia trachomatis

*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 moxifloxacin ophthalmic solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled 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 list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of 2 microgram/mL or less (systemic susceptible breakpoint) against most (greater than or equal to 90%) strains of the following ocular pathogens.

Aerobic Gram-Positive Microorganisms

Listeria monocytogenes

Staphylococcus saprophyticus

Streptococcus agalactiae

Streptococcus mitis

Streptococcus pyogenes

Streptococcus Group C, G, and F

Aerobic Gram-Negative Microorganisms

Acinetobacter baumanni

Acinetobacter calcoaceticus

Citrobacter freundi

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiela oxytoca

Klebsiela pneumoniae

Moraxela catarrhalis

Morganela morgani

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Pseudomonas stutzeri

Anaerobic Microorganisms

Clostridium perfringens

Fusobacterium species

Prevotela species

Propionibacterium acnes

Other Microorganisms

Chlamydia pneumoniae

Legionella pneumophila

Mycobacterium avium

Mycobacterium marinum

Mycoplasma pneumoniae.

CLINICAL STUDIES

In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, moxifloxacin ophthalmic solution produced clinical cures on Day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of baseline pathogens ranged from 84% to 94%.

In a randomized, double-masked, multicenter, parallel-group clinical trial of pediatric patients with bacterial conjunctivitis between birth and 31 days of age, patients were dosed with moxifloxacin ophthalmic solution or another anti-infective agent. Clinical outcomes for the trial demonstrated a clinical cure rate of 80% at Day 9 and a microbiological eradication success rate of 92% at Day 9.

5.3. Pharmacokinetic properties

Plasma concentrations of moxifloxacin were measured in healthy adult male and female subjects who received bilateral topical ocular doses of moxifloxacin ophthalmic solution 3 times a day. The mean steady-state C max (2.7 ng/mL) and AUC (41.9 ng●hr/mL) values were

1600 and 1100 times lower than the mean C 0-∞ max and AUC reported after therapeutic 400 mg doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis

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 (3224 times the highest recommended total daily human ophthalmic dose for a 60 kg person, based on body surface area).

Mutagenesis

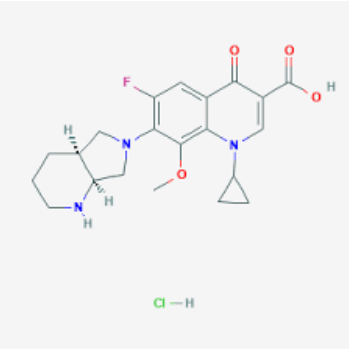
Moxifloxacin was not mutagenic in four bacterial strains used in the Ames Salmonella reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT 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.

Impairment of Fertility

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 3224 times the highest recommended total daily human ophthalmic dose, based on body surface area. At 500 mg/kg/day orally, there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

7. Description

Moxifloxacin Hydrochloride is 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4as,7as)-octahydro-6H-pyrolo'3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride. The empirical formula is $C_{21}H_{25}ClFN_3O_4$, and its molecular weight is 437.9 g/mol. The chemical structure of Moxifloxacin Hydrochloride is:



MOXIF

Moxifloxacin Eye Drops are yellow coloured, clear liquid.

The List of Excipients used are Sodium Chloride, Borax, Boric Acid, Benzalkonium Chloride Solution and Hydroxy Propyl Methyl Cellulose.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

MOXIF is available in pack of 10 ml vial.

8.4. Storage and handing instructions

Store at a temperature not exceeding 30ºC, Protected from light.

Keep the medicine out of reach of children.

Shake well before use.

Not for Injection

For External use only.

Replace the cap after every use.

This drug may cause low blood sugar and mental health related side effects.

Warnings:

1. If irritation persists or increases, discontinue the use and consult the physician.
2. Do not touch the vial tip to any surface since this may contaminate the solution.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

East African (India) overseas

Plot No. 8, Pharmacity, Selaqui,

Dehradun, 248011, (U.K.)

11. Details of permission or licence number with date

Mfg. Lic. No. is 94/UA/SC/P-2009, issue date is 10.11.2020.

12. Date of revision

NA

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