

CENTAFLOX Dx[®] Eye Drops

Composition:

Each ml of drop contains:

Moxifloxacin..... 0.5%

Dexamethasone..... 0.1%

PHARMACEUTICAL INFORMATION –

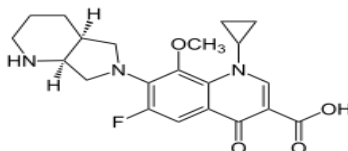
MOXIFLOXACIN

Generic name: Moxifloxacin

Chemical name: 1-Cyclopropyl-7-[(1S,6S)-2,8-diazabicyclo[4.3.0]nonan-8-yl]-6-fluoro-8-methoxy-4-oxoquinoline-3-carboxylic acid

Molecular mass: 401.431 g/mol

Structural formula:



Empirical formula – C₂₁H₂₄FN₃O₄

Storage and Stability:

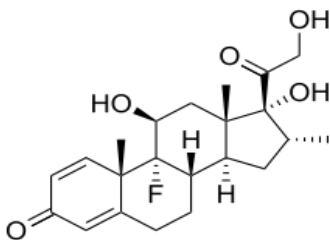
DEXAMETHASONE

Generic name: Dexamethasone

Chemical name: (8S,9R,10S,11S,13S,14S,16R,17R)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[*a*]phenanthren-3-one

Molecular mass: 392.461 g/mol

Structural formula:



Empirical Formula: C₂₂H₂₉FO₅

Mechanism of Action

MOXIFLOXACIN

The fluoroquinolones are the only direct inhibitors of DNA synthesis; by binding to the enzyme-DNA complex, they stabilize DNA strand breaks created by DNA gyrase and topoisomerase IV. Ternary complexes of drug, enzyme, and DNA block progress of the replication fork. Cytotoxicity of fluoroquinolones is likely a 2-step process involving (1) conversion of the topoisomerase-quinolone-DNA complex to an irreversible form and (2) generation of a double-strand break by denaturation of the topoisomerase.

Moxifloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication.

DEXAMETHASONE

Dexamethasone is a potent, long-term acting synthetic glucocorticoid class of steroid drugs that have anti-inflammatory and immunosuppressant properties.

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems. At equipotent anti-inflammatory doses (inhibition of Phospholipase A2), dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

Pharmacokinetics

MOXIFLOXACIN

Following topical ocular administration of moxifloxacin ophthalmic solution, moxifloxacin was absorbed into the systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female adult subjects who received bilateral topical ocular doses of moxifloxacin solution every 8 hours for a total of 13 doses. The mean steady-state C_{max} and AUC were 2.7 ng/mL and 41.9 ngAhr/mL, respectively. These systemic exposure values were at least 1,600 and 1,000 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours. Moxifloxacin is widely distributed in the body and is excreted in feces or urine either unchanged or as glucuronide or sulfate conjugates. Tear film concentrations were studied in 31 healthy

male and female adult volunteers who were administered 1 drop of moxifloxacin solution to both eyes every 8 hours for a total of 10 doses. Mean tear concentrations at 5 minutes following the first and last topical dose were 46.0 and 55.2:µg/mL, respectively. Thereafter, they decline rapidly in a biphasic manner with the means ranging approximately 1 to 4 µg/mL over the 1 to 8 hour sampling period. Pre-dose morning tear concentrations on Days 2 to 4 averaged over 4 µg/mL. Studies conducted in animals indicate penetration into the conjunctiva and ocular tissues with prolonged binding to melanin.

DEXAMETHASONE

Absorption

When given topically to the eye, dexamethasone is absorbed into the aqueous humour, cornea, iris, choroid, ciliary body and retina. Systemic absorption occurs but may be significant only at higher dosages or in extended paediatric therapy. Up to 90% of dexamethasone is absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide individual variations.

Distribution

Tissue distribution studies in animals show a high uptake of dexamethasone by the liver, kidney and adrenal glands; a volume of distribution has been quoted as 0.58 l/kg. In man, over 60% of circulating steroids are excreted in the urine within 24 hours, largely as unconjugated steroid.

Biotransformation

Dexamethasone sodium phosphate is rapidly converted to dexamethasone within the circulation. Up to 77% of dexamethasone is bound to plasma proteins, mainly albumin. This percentage, unlike cortisol, remains practically unchanged with increasing steroid concentrations. The mean plasma half-life of dexamethasone is 3.6 ± 0.9 h.

Elimination

Dexamethasone also appears to be cleared more rapidly from the circulation of the foetus and neonate than in the mother; plasma dexamethasone levels in the foetus and the mother have been found in the ratio of 0.32:1.

Pharmacodynamics

MOXIFLOXACIN

Moxifloxacin is an 8-methoxy fluoroquinolone with a diazabicyclononyl ring at the C7 position. 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.

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.

DEXAMETHASONE

Dexamethasone is a highly potent and long-acting glucocorticoid. It has an approximately 7 times greater anti-inflammatory potency than prednisolone, another commonly prescribed corticosteroid.

The actions of corticosteroids are mediated by the binding of the corticosteroid molecules to receptor molecules located within sensitive cells. Corticosteroid receptors are present in human trabecular meshwork cells and in rabbit iris ciliary body tissue.

Corticosteroids will inhibit phospholipase A2 thereby preventing the generation of substances which mediate inflammation, for example, prostaglandins. Corticosteroids also produce a marked, though transient, lymphocytopenia. This depletion is due to redistribution of the cells, the T lymphocytes being affected to a greater degree than the B lymphocytes. Lymphokine production is reduced, as is the sensitivity of macrophages to activation by lymphokines. Corticosteroids also retard epithelial regeneration, diminish post-inflammatory neo-vascularisation and reduce towards normal levels the excessive permeability of inflamed capillaries.

The actions of corticosteroids described above are exhibited by dexamethasone and they all contribute to its anti-inflammatory effect.

Indications

- Treatment of ocular infections caused by susceptible microorganisms.
- Prevention of inflammation & bacterial infection after ocular surgery.

Dosage and Administration

- Ocular infections caused by susceptible organisms Instill 1 drop qid for 7 days.
- Prevention of postop ocular inflammation & infection: Instill 1 drop qid in the eye, starting 1 day pre-operation & during 15 days post-operation.

Contraindications

Hypersensitivity to any active ingredient or other quinolones or any other excipients

Warnings

MOXIFLOXACIN

For ocular use only

- Moxifloxacin ophthalmic solution is not for injection into the eye. Moxifloxacin solution should not be injected sub-conjunctively, nor should it be introduced directly into the anterior chamber of the eye. In patients receiving systemically administered 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 moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment.
- Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson Syndrome), vasculitis, arthralgia, myalgia, serum sickness, allergic pneumonitis, interstitial nephritis, acute renal insufficiency or failure, hepatitis, jaundice, acute hepatic necrosis or failure, anemia including hemolytic and aplastic, thrombocytopenia including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities.

DEXAMETHASONE

- Stress and intercurrent illness in patients on corticosteroid therapy subjected to unusual stress (from trauma or infection), increased dosage of rapidly acting corticosteroids before, during & after the stressful situation is indicated.
- Adrenocortical Insufficiency Drug induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimised by gradual reduction of dosage.
- Infection Corticosteroids may mask some signs of infection (such as fever and inflammation), and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used.
- Ophthalmological Complications Prolonged use of corticosteroids may produce posterior subcapsular cataracts or glaucoma with possible damage to optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

- Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Precautions

MOXIFLOXACIN

- **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 bio-microscopy, and, where appropriate, fluorescein staining. In general, patients with signs and symptoms of bacterial conjunctivitis should be advised not to wear contact lenses.
- Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. Treatment with Moxifloxacin should be discontinued at the first sign of tendon inflammation. There are no studies on the effect of ocular administration of moxifloxacin on fertility.
- Moxifloxacin may cause temporary blurred vision or other visual disturbances, which may affect the ability to drive or use machines. If blurred vision occurs at application, the patient must wait until the vision clears before driving or using machinery.
- Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source. Systemically administered 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. The potential of moxifloxacin ophthalmic solution to produce arthropathy in animals has not been studied. Moxifloxacin and other members of the quinolone class have been shown to cause arthropathy in immature Beagle dogs following oral administration.

DEXAMETHASONE

- During prolonged corticosteroid therapy, adrenal suppression and atrophy may occur and secretion of corticotrophin may be suppressed. Abrupt withdrawal of corticosteroid therapy may precipitate acute adrenal insufficiency with muscle weakness, hypotension, hypoglycaemia, headache, nausea, vomiting, restlessness and muscle and joint pain.

- Muscle weakness and stiff joints may persist for three to six months after discontinuation of treatment. In some cases, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been under treatment.
- Use with caution in patients with impaired hepatic function, a reduction of dosage may be necessary. In treating chronic active liver disease with the drug, major adverse reactions such as vertebral collapse, diabetes, hypertension, cataracts and Cushing's syndrome occur in about 30% of patients.
- Caution is recommended for elderly patients as they are more susceptible to adverse reactions.
- The possibility of development of osteoporosis should be an important consideration in initiating and managing corticosteroid therapy, especially in post-menopausal women. Caution should be taken in patients with diabetes mellitus.
- Patients should not be vaccinated with live vaccines while on corticosteroid therapy. Other immunization procedures should not be undertaken in patients on corticosteroid therapy, especially on high doses, because of possible hazards of neurological complications and lack of antibody response.
- Immunization procedures may be undertaken in patients receiving corticosteroids as replacement therapy.
- Use in Pregnancy: Category A of Australian Categorisation of Risk of Drug Use in Pregnancy. In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations) and abortion.
- Use in Lactation: Glucocorticoids appear in breast milk in small quantities. Mothers taking high doses of glucocorticoids should be advised against breast feeding.
- Use in Children: Children on long term steroids must be carefully observed for potential serious adverse reactions such as obesity, growth retardation, osteoporosis and adrenal suppression.
- Interactions with other medicines: Drugs which induce hepatic microsomal enzymes, such as barbiturates, phenytoin and rifampicin, administered before or during treatment may shorten the elimination half-life of the drug. Long term corticosteroid therapy may also reduce the half-life. Oral contraceptives have been reported to increase the volume of distribution.

Adverse Effects

- Glaucoma w/ optic nerve damage
- Visual acuity & field defects
- Cataract formation
- Secondary ocular infection
- Perforation of the globe

- Decreased visual acuity
- Ocular discomfort, hyperemia, pain & pruritus
- Subconjunctival hemorrhage
- Tearing

Drug Interactions

MOXIFLOXACIN

Drug-drug interaction studies have not been conducted with moxifloxacin solution. Moxifloxacin can be chelated by polyvalent ions such as Mg⁺⁺, Al⁺⁺⁺, Fe⁺⁺ and Zn⁺⁺. There is limited information available on the concurrent use of moxifloxacin solution and other ophthalmic products. Following oral administration, no clinically significant drug-drug interactions between theophylline, warfarin, digoxin, oral contraceptives or glyburide have been observed with moxifloxacin. Theophylline, digoxin, probenecid, and ranitidine have been shown not to alter the pharmacokinetics of moxifloxacin. 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.

DEXAMETHASONE

The risk of increased intraocular pressure associated with prolonged corticosteroid therapy may be more likely to occur with concomitant use of anticholinergics, especially atropine and related compounds, in patients predisposed to acute angle closure.

The risk of corneal deposits or corneal opacity may be more likely to occur in patients presenting with compromised cornea and receiving polypharmacy with other phosphate-containing eye medications.

The following drug interactions are possible, but are unlikely to be of clinical significance, following the use of Dexamethasone:

The therapeutic efficacy of dexamethasone may be reduced by phenytoin, phenobarbitone, ephedrine and rifampicin.

Glucocorticoids may increase the need for salicylates as plasma salicylate clearance is increased.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

OVERDOSAGE

MOXIFLOXACIN

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdose it is recommended that appropriate supportive

care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose. Contact Poisons Information Centre 131126 for advice on management.

DEXAMETHASONE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. The oral LD50 of dexamethasone in female mice was 6.5 g/kg. The intravenous LD50 of dexamethasone sodium phosphate in female mice was 794 mg/kg.

SHELF-LIFE -

PACKAGING INFORMATION -