NOVARTIS

Moxifloxacin hydrochloride Dexamethasone phosphate

Vigadexa*

5 mg /1 mg per mL

Sterile Ophthalmic Solution

Antibacterial/ Anti-inflammatory

Description and composition

Pharmaceutical form

Sterile Ophthalmic Solution

Active substances

1 mL of solution contains 5 mg moxifloxacin (equivalent to 5.45 mg moxifloxacin hydrochloride) and 1 mg dexamethasone (equivalent to 1.1 mg dexamethasone sodium phosphate).

Excipients

Sodium chloride, boric acid, sorbitol, tyloxapol, disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

Indications

Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution is indicated in the treatment of ocular infections caused by susceptible microorganisms and in the prevention of inflammation and bacterial infection that may occur after ocular surgery.

Dosage regimen and administration

Dosage regimen

To prevent post-surgical ocular inflammation and infection:

- Instill 1 drop 4 times per day in the eye to be operated on, starting 1 day before the surgery and for 15 days after the surgery.
- In patients who have undergone cataract surgery, instill the solution immediately after the surgery.
- In patients who have undergone refractive surgery by LASIK, instill the solution within 15 minutes after the surgery.

In ocular infections caused by susceptible organisms:

- Instill 1 drop 4 times per day for 7 days.

Method of administration

For ocular use only.

- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using product. *[Only applicable for Eye Drop containing a snap collar]*
- If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointment should be administered last.
- Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via ocular route and result in a decrease in systemic adverse reactions.

Contraindications

- Hypersensitivity to the active substances, any of the excipients or other quinolones.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral infections of cornea or conjunctiva.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- Mycobacterial ocular infections.

Warnings and precautions

- In patients receiving systemic quinolones, 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 moxifloxacin occurs, discontinue use of product. Serious acute hypersensitivity reactions require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.
- Prolonged use of ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual field defects, and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure should be checked routinely and frequently. This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults.
- The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).
- Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy. Therefore, treatment with Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution should be discontinued at the first sign of tendon inflammation (see section 7 Adverse drug reactions).
- Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ophthalmic dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat) (see section 8 Interactions). In these cases, treatment should not be discontinued abruptly, but progressively tapered.

- Corticosteroids may reduce resistance to and aid in the establishment of nonsusceptible bacterial, fungal, viral or parasitic infections and mask the clinical signs of infection.
- Fungal infection should be suspected in patients with persistent corneal ulceration. Corticosteroids therapy should be discontinued if fungal infection occurs.
- Topical ophthalmic corticosteroids may slow corneal wound healing. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems (see section 8 Interactions).
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
- Prolonged use of antibiotics may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

Adverse drug reactions

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 0-1 Frequency of adverse drug reactions in clinical trials

System organ class	Adverse reactions	Frequency category
Psychiatric disorders	Insomnia	Rare
Nervous system disorders	Dysgeusia	Uncommon
Eye disorders	Eye pruritus, eye irritation	Common
	Vision blurred, eyelid pain	Uncommon
Respiratory thoracic and mediastinal disorders	Oropharyngeal pain	Uncommon

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 0-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ class	Adverse reactions
Eye disorders	Ocular hyperaemia

Interactions

- Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.
- CYP3A4 inhibitors, including ritonavir and cobicistat, may increase systemic exposure resulting in increased risk of adrenal suppression/Cushing's syndrome. (see section 6 Warnings and precautions). The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

There are no adequate and well-controlled studies with Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution in pregnant women to inform a product-associated risk.

Prolonged or repeated systemic corticosteroids use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Embryo-fetal toxicity and teratogenicity were seen in animal studies with dexamethasone, both after systemic and ocular administration at therapeutic dose levels (see Animal data).

Oral administration of moxifloxacin to rats and monkeys and intravenously to rabbits during the period of organogenesis did not produce adverse maternal or fetal effects at 30 times higher than the maximum recommended ophthalmic human dose (MROHD) based on area under the curve (AUC) (see Animal data).

Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Animal data

Dexamethasone

In embryo fetal development studies, dexamethasone was teratogenic in mice and rabbits following topical ocular application. In mice, rats and rabbits, a number of fetal malformations, fetal growth retardation, and increased mortality rates were seen at maternal toxic doses following systemic administration (oral, subcutaneous, and intramuscular) during the period of organogenesis. The overall no-observed-effect level (NOEL) for developmental toxicity was derived from an (oral) rat study and was based on embryotoxicity (0.01 mg/kg/day). This corresponds to less than 1 time the MROHD based on body surface area (BSA).

Moxifloxacin

Embryofetal 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 higher than MROHD based on AUC). No-observed-adverse-effect-level (NOAEL) for developmental toxicity was 100 mg/kg/day (30 times higher than MROHD based on AUC).

Embryofetal studies were conducted in pregnant rabbits administered with 2, 6.5 or 20 mg/kg/day moxifloxacin by intravenous route on gestation days 6 to 20, to target the period of organogenesis. Abortions, increased fetal malformations, delayed fetal skeletal ossification, and reduced placental and fetal body weights were observed at 20 mg/kg/day (1086 times higher than MROHD based on AUC), a dose that produced maternal body weight loss and death.. The NOAEL for developmental toxicity was 6.5 mg/kg/day (246 times higher than MROHD based on AUC).

Pregnant cynomolgus monkeys were administered moxifloxacin at doses of 10, 30 or 100 mg/kg/day by intragastric intubation between gestation days 20 to 50, targeting the period of organogenesis. At the maternal toxic doses of ≥ 30 mg/kg/day, increased abortions, vomiting and diarrhea were observed. Smaller fetuses with reduced fetal body weights were observed at 100 mg/kg/day (2864 times higher than MROHD based on AUC). The NOAEL for fetal toxicity was 10 mg/kg/day (174 times higher than MROHD based on AUC).

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 increase in the duration of pregnancy, reduced pup birth weight, and decreased prenatal and neonatal survival were observed at 500 mg/kg/day (277 times higher than MROHD based on AUC). The NOAEL for pre- and postnatal development was 100 mg/kg/day (30 times higher than MROHD at AUC).

Lactation

Risk summary

It is not known if moxifloxacin and dexamethasone are transferred into human milk following topical ocular administration. A study in lactating rats has shown transfer of moxifloxacin into milk following oral administration (see Animal data).

It is not likely that the amount of moxifloxacin and dexamethasone would be detectable in human milk or be capable of producing clinical effects in the infant following topical ocular use of the product. However, a risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Animal data

No nonclinical studies have been conducted with dexamethasone in lactating animals. Following oral administration of 5 mg/kg ^{14}C-moxifloxacin to lactating rats, the amount of radioactivity was lower in milk than plasma. No radioactivity was detected in milk after 24 hours.

Females and males of reproductive potential

There are no data regarding the effects of Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution on human or animal fertility. There is limited clinical data to evaluate the effect of moxifloxacin or dexamethasone on male or female fertility. No standard animal fertility studies are available with dexamethasone. Moxifloxacin did not impair fertility in rats.

Overdosage

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, nor in the event of accidental ingestion of the contents of one bottle.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Corticosteroids and anti-infectives in combination

ATC code: S01CA01

Mechanism of action (MOA)

Moxifloxacin/ Dexamethasone is an isotonic and sterile ophthalmic solution combining moxifloxacin hydrochloride and dexamethasone disodium phosphate. Subjects who may benefit from the topical combined therapy with an antibacterial agent and an anti-inflammatory agent are those who have undergone ocular surgery, such as cataract extraction and refractive surgery. Instillation of 1 steroid and 1 associated antibiotic is beneficial in these subjects in the following manner: the steroid suppresses inflammation, while the antibiotic controls the proliferation of potentially pathogenic susceptible bacteria, and also works in a prophylactic way. Many bacterial species found in post-surgical endophthalmitis are the same species generally found in the periocular flora.

Moxifloxacin, a fourth-generation fluoroquinolone, inhibits the DNA gyrase and topoisomerase IV required for bacterial DNA replication, repair, and recombination. Dexamethasone is a moderately powerful corticosteroid having good penetration in ocular tissue. Corticosteroids have an anti-inflammatory as well as a vasoconstrictive effect. They suppress the inflammatory response and symptoms in various disorders without basically curing these disorders.

The exact mechanism of anti-inflammatory action of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects.

Dexamethasone is one of the most potent corticosteroids with a relative anti-inflammatory potency greater than prednisolone or hydrocortisone.

Mechanisms of Resistance

Resistance to fluoroquinolones, including moxifloxacin, occurs generally by chromosomal mutations in genes encoding DNA gyrase and topoisomerase IV. In Gram-negative bacteria, moxifloxacin resistance can be due to mutations in the multiple antibiotic resistance and quinolone resistance gene systems. Cross-resistance with beta-lactams, macrolides and aminoglycosides is not expected due to differences in mode of action.

Breakpoints

The minimal inhibitory concentration (MIC) breakpoints (mg/L) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows (where S = susceptibility and R = resistance):

- Staphylococcus species $S \leq 0.5$, $R > 1$
- Streptococcus A,B,C,G $S \leq 0.5$, $R > 1$
- Streptococcus pneumoniae $S \leq 0.5$, $R > 0.5$
- Haemophilus influenzae $S \leq 0.5$, $R > 0.5$
- Moraxella catarrhalis $S \leq 0.5$, $R > 0.5$
- Enterobacteriaceae $S \leq 0.5$, $R > 1$
- Not species-related $S \leq 0.5$, $R > 1$

The *in vitro* breakpoints have been useful in predicting clinical efficacy of moxifloxacin when administered systemically. These breakpoints might not be applicable on topical ocular use of the medicinal product as higher concentrations are obtained in the eye and the local physical/chemical circumstances can influence the activity of the product on the site of administration.

Clinical efficacy against specific pathogens

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of moxifloxacin in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive micro-organisms:

Corynebacterium species including Corynebacterium diphtheriae

Staphylococcus aureus methicillin susceptible

Streptococcus pneumoniae Streptococcus pyogenes Streptococcus viridans Group

Aerobic Gram-negative micro-organisms:

Enterobacter cloacae Haemophilus influenzae Klebsiella oxytoca Moraxella catarrhalis Serratia marcescens

Anaerobic micro-organisms: Proprionibacterium acnes

Other micro-organisms:

Chlamydia trachomatis

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms:

Staphylococcus aureus methicillin resistant

Staphylococcus coagulase negative species methicillin resistant

Aerobic Gram-negative micro-organisms:

Neisseria gonorrhoeae

Inherently resistant organisms

Aerobic Gram-negative micro-organisms:

Pseudomonas aeruginosa

Pharmacokinetics (PK)

The systemic pharmacokinetics of moxifloxacin and dexamethasone has not been studied in humans following topical ocular dosing of Moxifloxacin Ophthalmic Solution, 0.5% or Gel. However, the pharmacokinetics of moxifloxacin and dexamethasone in humans has been well characterized following oral, intravenous and topical ocular administration.

Absorption

Moxifloxacin: The corneal penetration of moxifloxacin was evaluated in adult cataract surgery patients after topical ocular administration of Moxifloxacin Ophthalmic Solution, 0.5%. Moxifloxacin readily penetrated the cornea and was well absorbed, achieving a mean maximum concentration (Cmax) of 1.61 ± 1.26 µg/mL in the aqueous humor within 2 hours post-dose following a 2 day QID dosing regimen (1 drop for 4 doses on the day prior to surgery and on the day of surgery) and a Cmax of 1.55 ± 0.71 µg/mL within 30 minutes postdose following a 1 day dosing regimen (1 drop every 15 minutes for 4 doses on the day of surgery). The plasma concentrations of moxifloxacin were measured in healthy subjects who received bilateral topical ocular doses of moxifloxacin ophthalmic solution 0.5% 3 times per day. The Cmax values at steady state (2.70 ± 1.29 ng/mL) and the estimated area under the curve (AUC0-∞;41.9 ± 15.6 ng•h/mL) were approximately 1667 and 917 times lower, respectively than the mean Cmax and AUC obtained following oral therapeutic doses of 400 mg of moxifloxacin. According to clinical pharmacokinetics study reported in the literature, oral absorption of moxifloxacin of healthy volunteers is rapid and the bioavailability is almost complete at 86%.

Dexamethasone: After topical ocular administration of dexamethasone 0.1% ophthalmic solution to patients undergoing cataract surgery, dexamethasone is detectable after 30 minutes in the aqueous humor and peaks at 90 to 120 minutes with a mean concentration of 31 ng/mL. Low but detectable concentrations are observed in the aqueous humor after 12 hours. Oral bioavailability of dexamethasone ranges from 70-80% in normal subjects and patients.

Distribution

Moxifloxacin: In humans, the volume of distribution at steady-state was approximately 2.0 L/kg. Moxifloxacin is approximately 48% bound to plasma proteins. The degree of protein binding was consistent across the range of concentrations in plasma tested (0.05 to 4.7 mg/L).

Dexamethasone: The volume of distribution in humans at steady state was 0.58 L/kg. In vitro, no change in human plasma protein binding was observed with dexamethasone concentrations from 0.04 to 4 μg/mL, with a mean plasma protein binding of 77.4%.

Biotransformation/metabolism

Moxifloxacin: Moxifloxacin undergoes both sulfation of the secondary amine (M1), major pathway and glucuronidation of the carboxyl group (M2), secondary pathway in man. Sulfation occurs on the secondary amine of moxifloxacin while glucuronidation occurs on the carboxylic acid to form an acyl glucuronide. N-sulfonate and the acyl glucuronide are approximately one-third and one- tenth of parent drug maximal concentration after oral administration. Substantial percentage of the acyl glucuronide exposure after oral administration is the result of first-pass phase II metabolism. Neither the N-sulfonate metabolite nor the acyl glucuronide appeared to be pharmacologically active.

Dexamethasone: After oral administration, two major metabolites have been identified of which 60% of the dose was 6β-hydroxydexamethasone and up to 10% was 6β-hydroxy-20-dihydrodexamethasone.

Elimination

Moxifloxacin: After both iv or oral routes of administration, the terminal half-lives of elimination are similar at approximately 12 hours. The total body clearance is slow at approximately 12 L/hr. About 20% of the dose is excreted unchanged in the urine and the renal clearance was 43 mL/min. Fecal excretion was found to be the major route of elimination. Both parent drug (25% of the dose) and the N-sulfonate metabolite (35% of the dose) accounted for 60% of the total dose in feces. The acyl glucuronide was not detected in feces after systemic administration. Urinary excretion accounted for another 35% of the total dose with 20% as parent drug, 15% as the N-sulfonate metabolite and 5% as the acyl-glucuronide metabolite and the renal clearance was 43 mL/min. Renal excretion is the result of glomerular filtration, active secretion (the acyl glucuronide metabolite) and tubular reabsorption.

Dexamethasone: After intravenous administration of dexamethasone, the systemic clearance was 0.125 L/hr/kg. After iv bolus administration, 2.6% of the unchanged parent drug was recovered in the urine, while up to 70% of the dose was recovered as identified metabolites. After systemic dosing, the half-life has been reported as 3-4 hours but was found to be slightly longer in males. This observed difference was not attributed to changes in systemic clearance but to differences in volume of distribution and body weight.

Linearity/non-linearity

Moxifloxacin: The pharmacokinetics of moxifloxacin were linear in the range of 50 to 800 mg following the administration of a single oral dose. The plasma concentration time curves followed very similar patterns for all doses, and no significant dose dependency was detectable.

Dexamethasone: Linear pharmacokinetics were observed after oral administration with doses between 0.5 to 1.5 mg where the AUC was less than proportional to the oral dose.

Pharmacokinetic/pharmacodynamic relationship(s)

A pharmacodynamic/pharmacokinetic relationship after topical ocular administration has not been established.

Special populations

Moxifloxacin: Moxifloxacin does not exhibit age- or gender-dependent pharmacokinetics comparing young and elderly healthy volunteers.

Pediatric patients (below 18 years)

Moxifloxacin: No pediatric pharmacokinetic results have been published.

Dexamethasone: Pediatric pharmacokinetics varied between age groups but wide interpatient variabilities were observed.

Renal impairment

Moxifloxacin: Dose adjustment of moxifloxacin does not appear to be necessary in those with renal dysfunction.

Dexamethasone: Pharmacokinetics of systemic dexamethasone did not significantly differ in renal-impaired patients when compared to normal subjects.

Hepatic impairment

Moxifloxacin: Dose adjustment of moxifloxacin does not appear to be necessary in those with mild to moderate hepatic impairment. The pharmacokinetics of moxifloxacin has not been studied in patients with severe hepatic insufficiency.

Pharmaceutical information

Incompatibilities

Not applicable.

Instructions for use and handling

No special requirements.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

AVAILABILITY: Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution is a colorless to greenish yellow solution.

It is supplied in a 5 mL LDPE Bottle in a box; 2.5 mL (Physician's Sample).

STORAGE:

Store at temperatures not exceeding 30˚C. Do not freeze.
Keep the bottle tightly closed when not in use.
Moxifloxacin/Dexamethasone (Vigadexa*) Sterile Ophthalmic Solution must be kept out of the reach and sight of children.

CAUTION: Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

PRODUCT FOR ADULT USE ONLY. CHILD USE MAY CAUSE RISK TO THE HEALTH.

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