1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VOXIDEX 5 mg/1 mg per 1 ml eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of VOXIDEX eye drops, solution, contains levofloxacin hemihydrate equivalent to 5 mg of levofloxacin and dexamethasone sodium phosphate equivalent to 1 mg of free dexamethasone.

One drop (about 30 µl) contains about 0,150 mg of levofloxacin and 0,03 mg of dexamethasone.

Preservative: Benzalkonium chloride 0,005 % *m/v*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

A clear, greenish-yellow solution, free from visible particles, with a pH of 7,0 to 7,4 and osmolality of 270 to 330 mOsm/Kg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VOXIDEX is indicated in adults for prevention and treatment of inflammation, and prevention of infection associated with cataract surgery.

4.2. Posology and method of administration

Posology

Adults

One drop instilled into the conjunctival sac directly after surgery, then every 6 hours thereafter. Duration of treatment is 7 days.

If one dose is missed, treatment should continue with the next dose as planned.

Re-evaluation of the patient to assess the need to continue the administration of corticosteroid eye drops as monotherapy is recommended after the completion of one week of therapy with VOXIDEX. The length of this treatment can depend on the patient's risk factors and outcome of surgery and must be determined by the doctor according to slit-lamp microscopic findings and depending on the severity of the clinical picture. A follow-up treatment with steroid eye drops should not normally exceed 2 weeks. However, care should be taken not to discontinue therapy prematurely.

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Special populations

Elderly population

No dosage adjustment in elderly patients is necessary.

Renal impairment

VOXIDEX has not been studied in patients with renal impairment.

Hepatic impairment

VOXIDEX has not been studied in patients with hepatic impairment.

Paediatric population

The safety and efficacy of VOXIDEX in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

Ocular use.

Administer one drop in the affected eye.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.

Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

4.3. Contraindications

- Hypersensitivity to levofloxacin or to other quinolones, to dexamethasone, or to other steroids, or to any of the excipients listed in section 6.1, e.g. benzalkonium.
- Herpes simples, keratitis, varicella and other viral disease of the cornea and conjunctiva.
- Mycobacterial infections of the eye caused by, but not limited to, acid-fast bacilli such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, or *Mycobacterium avium*.
- Fungal diseases of ocular structures.
- Untreated purulent infection of the eye.

4.4. Special warnings and precautions for use

Ocular effects

VOXIDEX is for ophthalmic use only. VOXIDEX must not be injected sub-conjunctively. The solution should not be introduced directly into the anterior chamber of the eye.

Prolonged use may induce antibiotic resistance with result of overgrowth of non-susceptible organisms, including fungi. If infection develops, discontinue use and institute alternative therapy. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Prolonged use of topical ophthalmic corticosteroids, as contained in VOXIDEX, may result in ocular hypertension/glaucoma. The intraocular pressure should be checked frequently while on treatment with VOXIDEX. The risk of corticosteroid-induced increase in the intraocular pressure is increased in predisposed patients (e.g. diabetes).

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision and/or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may be related to complications to cataract surgery, development of glaucoma and/or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids, as contained in VOXIDEX.

Topical ophthalmic corticosteroids, as contained in VOXIDEX, may slow corneal wound healing. Topical ocular NSAIDs are also known to slow or delay healing. Concomitant

use of topical ocular NSAIDs and steroids may increase the potential for healing problems.

In those diseases causing thinning of the cornea or sclera, perforations have been reported to occur with the use of topical corticosteroids, as contained in VOXIDEX.

Systemic effects

Fluoroquinolones as contained in VOXIDEX have been associated with hypersensitivity reactions, even following a single dose. Discontinue VOXIDEX if an allergic reaction occurs.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including levofloxacin, particularly in older patients and those treated concurrently with corticosteroids. Therefore, caution should be exercised and treatment with VOXIDEX should be discontinued at the first sign of tendon inflammation.

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular 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). In these cases, treatment should be progressively discontinued.

Effects on immune system

Prolonged use with VOXIDEX should be avoided as the immune system may be suppressed. No long-term safety data is available for VOXIDEX.

Prolonged use (generally observed within 2 weeks of treatment) may also result in secondary ocular infections (bacterial, viral, or fungal) due to suppression of host response or to the delay of their healing. In addition, topical ocular corticosteroids may promote, aggravate or mask signs and symptoms of eye infections caused by

opportunistic microorganisms. Occurrence of these conditions is limited in case of short term corticosteroid treatment such as the one suggested for VOXIDEX (see section 4.2).

Paediatric population

VOXIDEX should not be used in patients under 18 years of age.

Excipients

This medicine contains 0,0015 mg benzalkonium chloride in each drop (about 30 µl) which is equivalent to 0,05 mg/ml.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.

4.5. Interaction with other medicines and other forms of interaction

No medicine interaction studies have been performed, and concomitant eye drops should be avoided.

The concomitant use of probenecid, cimetidine, or ciclosporin with levofloxacin altered some pharmacokinetic parameters of levofloxacin.

Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

CYP3A4 inhibitors (including ritonavir and cobicistat) may decrease dexamethasone clearance resulting in increased effects.

4.6. Fertility, pregnancy and lactation

The safety of VOXIDEX in pregnancy and lactation has not been established.

Pregnancy

VOXIDEX should not be used during pregnancy as there are no safety data.

Breastfeeding

Levofloxacin and dexamethasone, as contained in VOXIDEX, are excreted in human milk. VOXIDEX should not be used during breastfeeding.

Fertility

There are no data on potential effects of VOXIDEX on fertility.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

4.8. Undesirable effects

a) Summary of the safety profile

In clinical studies, 438 patients have been treated with VOXIDEX. Ocular disorders (e.g. corneal oedema, eye irritation, abnormal sensation in eye, lacrimation increased, asthenopia, corneal disorder, dry eye, eye pain, ocular discomfort, uveitis, visual brightness, conjunctivitis) have been reported. These reactions can also be linked to the cataract surgery itself. No serious adverse event was related to study treatment.

b) Tabulated list of adverse reactions

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders				Extra-ocular allergic reactions, including skin rash#	Anaphylaxis#	
Endocrine disorders					Depression of adrenal function~	Cushing's syndrome~, adrenal suppression~
Nervous system disorders			Headache*#, dysgeusia*			
Eye disorders	Ocular burning#, decreased vision and mucous strand#, increase of the intraocular pressure~	Discomfort~, irritation~, burning~, stinging~, itching~ and blurred vision~	Eye irritation*, abnormal sensation in eye*, ocular hypertension*, lid matting#, chemosis#, conjunctival papillary reaction#, lid oedema#, ocular discomfort#, ocular itching#, ocular pain#, conjunctival injection#, conjunctival follicles#, ocular dryness#, lid erythema#, photophobia#,allergic and hypersensitivity reactions~, delayed wound healing~, posterior subcapsular cataract~, opportunistic infections~, glaucoma		Conjunctivitis~, mydriasis~, ptosis~, corticosteroid-induced uveitis~, corneal calcifications~, crystalline keratopathy~, changes in corneal thickness~, corneal oedema~, corneal ulceration~ corneal perforation~	

Respiratory, thoracic and mediastinal disorders			Rhinitis#	Laryngeal oedema#		
Gastrointestinal disorders			Nausea*, tongue disorder*			
Skin and subcutaneous tissue disorders			Pruritis*			
General disorders and administrative site conditions					Face oedema~, administration site conditions ~	
Investigations			Increased intraocular pressure*+			

+ > 6 mmHg that means significant intraocular pressure increase.

* Reported with the combination of levofloxacin/dexamethasone.

Reported with the use of levofloxacin.

~ Reported with the use of dexamethasone.

c) Description of selected adverse reactions

Increase of the intra-ocular pressure (IOP) and glaucoma may occur. The use of corticosteroid treatment may result in ocular hypertension/glaucoma (especially for patients with previous IOP induced by steroids or with pre-existing high IOP or glaucoma). Children and elderly patients may be particularly susceptible to steroid-induced IOP rise (see section 4.4). Diabetics are also more prone to develop subcapsular cataracts following prolonged topical steroid administration.

Increase of the intra-ocular pressure induced by topical treatment with corticosteroids has been generally observed within 2 weeks of treatment (see section 4.4.).

Discomfort, irritation, burning, stinging, itching and blurred vision frequently may occur immediately after instillation. These events are usually mild and transient and have no consequences.

In diseases causing thinning of the cornea, topical use of steroids could lead to cornea perforation in some cases (see section 4.4).

Depression of adrenal function associated with systemic absorption of VOXIDEX may occur when the instillations are administered with a frequent dosing schedule.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

The total amount of levofloxacin and dexamethasone 21-Phosphate in vial of VOXIDEX is too small to induce toxic effects after an accidental oral intake.

Treatment

In the case of topical overdose, the treatment should be stopped. In case of prolonged irritation, the eye(s) should be rinsed with sterile water. The symptomatology due to accidental ingestion is not known. The medical practitioner may consider emesis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A.15.3 Combination antibiotics and/or sulphonamides and corticosteroids.

Pharmacotherapeutic group: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination

ATC code: S01C A01

Mechanism of action

VOXIDEX is a fixed dose combination of two active substances: levofloxacin and dexamethasone. These two active substances have a completely different mechanism of action being a topically combination of an antibiotic and a corticosteroid. Dexamethasone is a steroid used in ophthalmic therapy, while levofloxacin is an antibiotic of the quinolone class that is characterized by a broad spectrum of action, with confirmed activity on, both Gram-positive and Gram-negative bacteria. VOXIDEX is used for ocular inflammation, after surgery when an antibiotic and a corticosteroid are indicated.

Levofloxacin:

As a fluoroquinolone antibacterial medicine, levofloxacin, that is the active L-isomer of ofloxacin, inhibits bacterial type II topoisomerases—DNA gyrase and topoisomerase IV. Levofloxacin preferentially targets DNA gyrase in Gram negative bacteria and

topoisomerase IV in Gram positive bacteria. The spectrum of activity against ocular pathogens includes aerobic Gram-positive microorganisms (e.g. *S. aureus* MSSA*, S. pyogenes, S. pneumoniae,* viridans group streptococci), aerobic Gram-negative bacteria (e.g. *E. coli, H. influenzae, M. catarrhalis, P. aeruginosa* community isolates), other organisms (e.g. *Chlamydia trachomatis*).

Dexamethasone:

The efficacy of corticosteroids for the treatment of inflammatory conditions of the eye is well established. Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules, cyclooxygenase I or II, and cytokine expression. This action culminates in a reduced expression of proinflammatory mediators and the suppression of adhesion of circulating leukocytes to the vascular endothelium, thereby preventing their migration into inflamed ocular tissue. Dexamethasone has marked anti-inflammatory activity with reduced mineralocorticoid activity compared with some other steroids and is one of the most potent anti-inflammatory medicines.

Clinical efficacy:

The efficacy of levofloxacin/dexamethasone has been investigated in a controlled study to evaluate the non-inferiority of the levofloxacin/dexamethasone vs. a standard treatment with a commercial formulation of tobramycin (0,5 %) and dexamethasone (0,1 %) eye drops for the prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults. The Investigator in charge of evaluating study parameters was blinded to treatment assignment. Patients who completed their cataract surgery without complications were assigned to levofloxacin/dexamethasone eye drops, 1 drop 4 times a day for 7 days, followed by dexamethasone 0,1 % eye drops, 1 drop 4

times a day, for an additional 7 days, or to reference tobramycin + dexamethasone eye drops, 1 drop 4 times a day for 14 days.

Data of efficacy were available in 395 patients given levofloxacin/dexamethasone and in 393 patients given the reference product after cataract surgery. After 14 days of treatment, the proportion of patients with no signs of inflammation (primary endpoint of the study) in the levofloxacin/dexamethasone followed by dexamethasone group compared to the tobramycin + dexamethasone group was 95,19 % vs. 94,91 %, respectively. The difference between the two proportions was 0,0028 (95 % CI: [-0,0275; 0,0331]), which demonstrated the non-inferiority of the test vs. reference treatment regimen. No occurrence of endophthalmitis was reported during the study for either group. Signs of anterior chamber inflammation were absent in levofloxacin/dexamethasone arm in 73,16 % at day 4 and in 85,57 % of patients at day 8 after surgery. In tobramycin + dexamethasone arm, signs of anterior chamber inflammation were absent in 76,84 % at day 4 and in 86,77 % of patients at day 8. Conjunctival hyperaemia was already absent at day 4 in 85,75 % in levofloxacin/dexamethasone treatment arm *vs.* 82,19 % in tobramycin + dexamethasone arm, respectively. The safety profile was similar in both groups.

5.2. Pharmacokinetic properties

Absorption

The ocular instillation of levofloxacin/dexamethasone results in absorption of both active ingredients to the ocular tissues and, at a much lower extent, to the systemic circulation. After instillation to rabbit eyes, the plasma concentrations of levofloxacin increase with the dose after both single and repeated administration. Low levels of dexamethasone sodium phosphate are measured in plasma. In fact, dexamethasone sodium phosphate is rapidly metabolised *in vivo* to dexamethasone, which is the active metabolite.

Dexamethasone exposure increases with the dose and after repeated doses a minor accumulation of both levofloxacin and dexamethasone is evident.

Distribution

Both levofloxacin and dexamethasone levels in ocular tissues (aqueous humour, cornea and conjunctiva) result to be higher than the maximum plasma levels after single and repeated doses. In particular, after 28-day treatment levofloxacin and dexamethasone levels in ocular tissues are 50 to 100-fold and 3 to 4-fold higher than the C_{max} in plasma, respectively.

One-hundred-twenty-five patients undergoing cataract surgery have been randomized to 3 groups: levofloxacin, dexamethasone and levofloxacin/dexamethasone. One drop of each medicine was administered 60 and 90 minutes before limbal paracentesis. The mean of the observed values for the concentration of levofloxacin was equal to 711,899 ng/mL (95 % CI: 595.538; 828.260) in the levofloxacin/dexamethasone group compared to 777,307 ng/mL (95 % CI: 617.220; 937.394) when levofloxacin was administered alone. The concentrations of levofloxacin in the aqueous humour are well above the minimum inhibitory concentrations for the ocular pathogens in levofloxacin's spectrum of activity. When levofloxacin/dexamethasone was administered dexamethasone reached an aqueous humour concentration of 11,774 ng/mL (95 % CI: 9,812; 13,736) compared to 16,483 ng/mL (95 % CI: 13,736; 18,838) when dexamethasone was administered alone.

Elimination

Both levofloxacin and dexamethasone are eliminated via urine.

5.3 Preclinical safety data

Preclinical effects were observed only at exposures considerably in excess of the maximum human exposure after instillation of levofloxacin/dexamethasone, indicating little relevance to clinical use. Gyrase inhibitors have been shown to cause growth disorders of weight bearing joints in animal studies. In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs after high oral doses.

Reproductive toxicity:

Levofloxacin is not teratogenic in animal studies. Dexamethasone after topical and systemic administration caused the formation of cleft palate, delayed foetal growth and foetal mortality at the same dose levels. Peri- and postnatal toxicity of dexamethasone was also observed.

Phototoxic potential:

Studies in the mouse after both oral and intravenous dosing showed levofloxacin to have phototoxic activity only at very high doses.

Dexamethasone doesn't show any potential phototoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzalkonium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic dodecahydrate, sodium citrate, sodium hydroxide / hydrochloric acid (for pH adjustment), water for injection

6.2. Incompatibilities

This medicine must not be mixed with other medicines.

6.3. Shelf life

Unopened: 24 months.

Discard within 28 days after first opening.

6.4. Special precautions for storage

Store at or below 30 °C, in original packaging.

For storage conditions after opening, see section 6.3.

6.5. Nature and contents of container

VOXIDEX is packaged in a white low-density polyethylene (LDPE) bottle, with a white low-density polyethylene (LDPE) dropper and sealed with a white high-density polyethylene (HDPE) screw cap. A sealed and labelled bottle, filled with 5 ml of the eye drops solution, is packed into an outer carton.

6.6. Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

54/15.3/0836

9. DATE OF FIRST AUTHORISATION

14 September 2021

10. DATE OF REVISION OF TEXT

18 September 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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