SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MOXIDROP, 5 mg/1 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5,45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ophthalmic Solution

A sterile, clear greenish yellow colour solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MOXIDROP is indicated for the topical treatment of bacterial conjunctivitis caused by susceptible organisms.

(See section 5.1 for susceptibility to moxifloxacin).

4.2 Posology and method of administration

Posology

Use in adults including the elderly:

Instil one drop in the affected eye(s) 3 times a day for 4 days.

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Use in children:

Moxifloxacin as in MOXIDROP has been shown to be safe and effective in paediatric patients including neonates and can be used at the same dose as in adults. There is no evidence that the ophthalmic administration of moxifloxacin as in MOXIDROP has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Use in hepatic and renal impairment:

Pharmacokinetic parameters of oral moxifloxacin were not significantly altered in patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B).

Studies were not performed in patients with severe hepatic impairment (Child Pugh Class C). Because of the low systemic exposure by the topical route of administration, no dosage adjustment of MOXIDROP is needed in patients with hepatic impairment.

The pharmacokinetic parameters of oral moxifloxacin are not significantly altered by mild, moderate or severe renal impairment. No dosage adjustment of moxifloxacin as in MOXIDROP is necessary in patients with renal impairment.

Method of administration

For ocular use only.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

4.3 Contraindications

MOXIDROP is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the excipients of MOXIDROP listed in 6.1.

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

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 oedema), airway obstruction, dyspnoea, urticaria, and itching (see section 4.8).

If an allergic reaction to MOXIDROP occurs, discontinue the use of MOXIDROP. Serious acute hypersensitivity reactions to moxifloxacin or any other product ingredient may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.

Prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including moxifloxacin, particularly in older patients and those treated concurrently with corticosteroids. Following ophthalmic administration of MOXIDROP plasma concentrations of moxifloxacin are much lower than after therapeutic oral doses of moxifloxacin (see section 4.5 and 5.2), however, caution should be exercised and treatment with MOXIDROP should be discontinued at the first sign of tendon inflammation (see section 4.8).

MOXIDROP should not be used for the prophylaxis or empiric treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum, because of the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae*. Patients with eye infections caused by *Neisseria gonorrhoeae* should receive appropriate systemic treatment.

Patients should be advised not to wear contact lenses if they have signs and symptoms of a bacterial ocular infection.

Paediatric population

Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

MOXIDROP is not recommended for the treatment of *Chlamydia trachomatis* in patients less than 2 years of age as it has not been evaluated in such patients. Patients older than 2 years of age with eye infections caused by *Chlamydia trachomatis* should receive appropriate systemic treatment.

4.5 Interaction with other medicines and other forms of interaction

No specific drug-drug interaction studies have been performed with MOXIDROP drops, they have been performed with the oral product at much higher systemic exposures than are achieved by the topical ocular route. Unlike some other fluoroquinolones, no clinically significant drug-drug interactions between systemically administered moxifloxacin and itraconazole, theophylline, warfarin, digoxin, oral contraceptives, probenecid, 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 metabolised by these cytochrome P450 isozymes. Given the low systemic concentration of moxifloxacin following topical ocular administration of the medicine (see Section 5.2), medicine interactions are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Pregnancy

Since there are no adequate and well-controlled studies of the use of moxifloxacin as in MOXIDROP in pregnant women, MOXIDROP should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

Animal studies have shown excretion of low levels in breast milk after oral administration of moxifloxacin. Moxifloxacin has not been measured in human milk although it can be presumed to be excreted in human milk. Caution should be exercised when MOXIDROP is administered to a nursing mother.

Fertility

No studies have been performed to evaluate the effect of ocular administration of moxifloxacin as in MOXIDROP on fertility.

4.7 Effects on ability to drive and use machines

MOXIDROP, 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

Summary of the safety profile

No serious ophthalmic or systemic undesirable effects related to the medicine were reported in clinical studies. The most frequently reported treatment-related undesirable effects with the medicine were eye irritation and eye pain.

Tabulated summary of adverse reactions

System Organ Classification	Frequency	Adverse reactions
Blood and lymphatic system disorders	*Less frequent*	Decreased haemoglobin
Immune system disorders	*Frequency unknown*	Hypersensitivity
Nervous system disorders	*Less frequent*	Headache, paraesthesia
	Frequency unknown	Dizziness
Eye disorders	*Frequent*	Eye pain, eye irritation, ocular discomfort (burning or stinging upon instillation)
	Less frequent	Punctate keratitis, dry eye, conjunctival haemorrhage, ocular hyperaemia, eye pruritus, eyelid oedema, corneal epithelium defect, corneal disorder, conjunctivitis, blepharitis, eye swelling, conjunctival oedema, blurred vision, reduced visual acuity, asthenopia, erythema of eyelid

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System Organ Classification	Frequency	Adverse reactions
	Frequency unknown	Endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, increased intraocular pressure, corneal opacity, corneal infiltrates, corneal deposits, eye allergy, keratitis, corneal oedema, photophobia, increased lacrimation, eye discharge, foreign body sensation in eyes
Cardiac disorders	*Frequency unknown*	Palpitations
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)
	Frequency unknown	Dyspnoea
Gastrointestinal disorders	*Less frequent*	Dysgeusia, vomiting
	Frequency unknown	Nausea
Hepato-biliary disorders	*Less frequent*	Increased alanine aminotransferase, increased gamma glutamyl transferase
Skin and subcutaneous tissue disorders	*Frequency unknown*	Erythema, rash, pruritus, urticaria

Paediatric population

Reports from clinical trials have shown that moxifloxacin as in MOXIDROP is safe in paediatric patients, including neonates. In patients under 18 years old, the two most frequent adverse reactions were eye irritation and eye pain.

Based on data from clinical trials involving paediatric patients, including neonates (see section 5.1), the type and severity of adverse reactions in the paediatric population are similar to those in adults.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pd.

4.9 Overdose

The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of MOXIDROP.

The total amount of moxifloxacin in a single container is too small to induce adverse effects after accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.1 Ophthalmic preparations with antibiotics and/or sulphonamides.

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives, other anti-infectives, ATC code: S01A E07.

Mechanism of Action

Moxifloxacin, a fourth-generation fluoroquinolone antibacterial agent active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens, typical microorganisms and anaerobes. It inhibits the DNA gyrase and topoisomerase IV required for bacterial DNA replication, repair, and recombination. The C8-methoxy moiety of moxifloxacin also lessens the selection of resistant mutants of Gram-positive bacteria.

Resistance

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

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)

Staphylococcus epidermidis

Staphylococcus hominis

Staphylococcus wameri

Streptococcus mitis Group

Streptococcus pneumoniae

Streptococcus pyogenes

Streptococcus viridans Group

Aerobic Gram-negative micro-organisms:

Acinetobacter species

Escherichia coli

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

Other micro-organisms:

None

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-negative micro-organisms:

Pseudomonas aeruginosa

Other micro-organisms:

None

5.2 Pharmacokinetic properties

Following topical ocular administration of moxifloxacin as in MOXIDROP, moxifloxacin was absorbed into the systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who received bilateral topical ocular doses of the medicine 3 times a day for 4 days. The mean steady-state

C_{max} and AUC were 2,7 ng/ml and 41,9 ng·hr/ml, respectively. These exposure values are approximately 1 600 and 1 200 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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure following administration to the eye indicating little relevance to clinical use.

Moxifloxacin was also genotoxic *in vitro* in bacteria and mammalian cells. As these effects can be traced to the interaction with bacterial gyrase and in considerably higher concentrations to the interaction with topoisomerase II in mammalian cells, a threshold level for genotoxicity can be assumed. In *in vivo* tests, no evidence of genotoxicity was found, despite high doses of moxifloxacin. The therapeutic doses for human use therefore provide adequate safety margin. No indication of a carcinogenic effect was observed in an initiation promotion model in rats.

Unlike other quinolones, moxifloxacin showed no phototoxic or photogenotoxic properties in extensive *in vitro* and *in vivo* studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid

Sodium chloride

Sodium hydroxide (pH adjuster)

Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Do not use more than 30 days after opening.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not use more than 30 days after opening the container at 25 °C (see section 6.3).

Keep bottle tightly closed when not in use.

6.5 Nature and contents of container

5 ml round LDPE dropper bottle for both 3 ml and 5 ml presentations. The product is stoppered with white

HDPE Screw Cap e-beam sterilised and LDPE droppers.

Pack size: box containing 1 bottle.

6.6 Special precautions for disposal and other handling

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

Do not use more than 30 days after opening the container at 25 °C (see section 6.3).

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8. REGISTRATION NUMBER

50/15.1/0350

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 November 2020

10. DATE OF REVISION OF THE TEXT

27 February 2022 (new proprietary name)