Approved Professional Information for Medicines for Human Use:

AVOXA EYE DROPS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AVOXA EYE DROPS 0,5 %

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AVOXA EYE DROPS 0,5 %

Each mL of solution contains 5,45 mg of moxifloxacin hydrochloride equivalent to 5,0 mg moxifloxacin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AVOXA EYE DROPS 0,5 %

Clear, yellow to yellow-green liquid solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVOXA EYE DROPS is indicated for the topical treatment of bacterial conjunctivitis caused by susceptible organisms. (See section 5.1).

4.2 Posology and method of administration

Posology

Dosage

Adults and the elderly

Instill 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.

Special population

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 low systemic exposure by the topical route of administration, no dosage adjustment of AVOXA EYE DROPS 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 AVOXA EYE DROPS is necessary in patients with renal impairment.

Paediatric population

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

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.

For new-born babies or children

In order to prevent the drops from being absorbed via the nasal mucosa, the nasolacrimal ducts should be held closed for 2 to 3 minutes with the fingers after administering the drops.

4.3 Contraindications

- Hypersensitivity to the moxifloxacin, to other quinolones, or to any of the excipients of AVOXA EYE DROPS listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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 AVOXA EYE DROPS occurs, discontinue use of the medicine. 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.

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.

Tendon inflammation

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 AVOXA EYE DROPS 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 AVOXA EYE DROPS should be discontinued at the first sign of tendon inflammation (see section 4.8).

AVOXA EYE DROPS should not be used for *Neisseria gonorrhoeae* eye infections

AVOXA EYE DROPS 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.

AVOXA EYE DROPS and contact lenses

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

Paediatric population

Data are very limited to establish efficacy and safety of AVOXA EYE DROPS in the treatment of conjunctivitis in neonates. Therefore, use of this medicine to treat conjunctivitis in neonates is not recommended.

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

AVOXA EYE DROPS 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 trachomitis* should receive appropriate systemic treatment.

4.5 Interaction with other medicines and other forms of interaction

No specific interaction studies have been performed with AVOXA EYE DROPS, solution. 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 or limited amount of data from the use of AVOXA EYE DROPS in pregnant women, it should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. However, no effects on pregnancy are anticipated since the systemic exposure to moxifloxacin is negligible.

Breastfeeding

Moxifloxacin has not been measured in human milk although it can be presumed to be excreted in human milk. Caution should be exercised when, AVOXA EYE DROPS is administered during breast feeding.

Fertility

Studies have not been performed to evaluate the effect of ocular administration of AVOXA EYE DROPS on fertility.

4.7 Effects on ability to drive and use machines

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

a) Summary of the safety profile

The most frequently reported treatment-related undesirable effects were eye irritation and eye pain, occurring at an overall incidence of 1 to 2 %. These reactions were mild in 96 % of those patients who experienced them, with only 1 patient discontinuing therapy as a result.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with moxifloxacin.

Frequency estimate:

Frequent (≥ 1/100)

Less frequent (< 1/100)

Not known (cannot be estimated from the available data)

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Blood and lymphatic system disorders		Haemoglobin decreased	
Nervous system disorders		Headache, paraesthesia	Dizziness
Eye disorders	Ocular pain, eye irritation	Punctate keratitis, dry eye, conjunctival haemorrhage, ocular hyperaemia, eye pruritus, eyelid oedema, ocular discomfort, corneal epithelium defect, corneal disorder, conjunctivitis, blepharitis, eye swelling, conjunctival oedema, vision blurred, visual acuity reduced, asthenopia, erythema of eyelid	Endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, intraocular pressure increased, corneal opacity, corneal infiltrates, corneal deposits, eye allergy, keratitis, corneal oedema, photophobia, eyelid oedema, lacrimation increased, eye discharge, foreign body sensation in eyes
Cardiac disorders			Palpitations

Respiratory, thoracic and mediastinal disorders		Nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)	Dyspnoea
Gastrointestinal disorders		Dysgeusia, vomiting	Nausea
Hepatobiliary disorders		Alanine aminotransferase increased, gammaglutamyltransferase increased	
Skin and subcutaneous tissue disorders			Erythema, rash, pruritus, urticaria

c. Description of selected adverse reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following first dose, have been reported in patients receiving systemic quinolone therapy. 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 4.4).

Ruptures of the shoulder, hand, Achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

d. Paediatric population

In clinical trials, AVOXA EYE DROPS has shown to be safe in paediatric patients, including neonates. In patients under 18 years old, the two most frequent adverse reactions were eye irritation and eye pain, both occurring at an incidence rate of 0,9 %. 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of AVOXA EYE DROPS. Intoxication after inadvertent oral ingestion can also be ruled out.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A.15.1 Ophthalmic preparations with antibiotics and/or sulphonamides

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives, other anti-infectives

ATC Code: S01A E07

Moxifloxacin is a fourth-generation fluoroquinonlone antibacterial agent active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens, atypical micro-organisms and anaerobes.

Mechanism of action

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms.

Moxifloxacin inhibits the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. The C-8-methoxy moiety of moxifloxacin also lessens the selection of resistant mutants of Gram-positive bacteria.

Mechanisms of Resistance

In vitro resistance to moxifloxacin develops slowly via multiple-step mutations and occurs at a general frequency between 10 – 9 to 10 – 11 for Gram-positive bacteria.

Fluoroquinolones, including moxifloxacin, differ in chemical structure and mode of action from beta-lactam antibiotics, macrolides and aminoglycosides, and therefore may be active against bacteria resistant to beta-lactam antibiotics, macrolides and aminoglycosides.

Breakpoints:

There are no official topical ophthalmic breakpoints for moxifloxacin and although systemic breakpoints have been used, their relevance to topical ophthalmic therapy is doubtful. The systemic breakpoint used for this antiobitic is S < 2 mg/ L, R > 4 mg/ L.

Susceptibility to Moxifloxacin

Commonly susceptible species (i.e., an MIC_{50} of < 4 mg/ L for at least 10 strains):

Aerobic Gram-positive microorganisms

Corynebacterium species

*Staphylococcus aureus**

*Slaphylococcus epidermidis**

Staphylococcus hominis

*Staphylococcus warneri**

Steptococcus rnitis Group*

*Streptococcus pneumoniae**

Steptococcus viridans Group*

Aerobic Gram-negative microorganisms

Acinetobacter species*

Escherichia coli

*Haemophilus influenzae**

Pseudomonas aeruginosa

Serratia marcescens

Other microorganisms

*Chlamydia trachomatis**

Species for which acquired resistance may be a problem:

Aerobic Gram-positive microorganisms: None

Aerobic Gram-negative microorganisms: None

Other microorganisms: None

*denotes those species which have been satisfactorily demonstrated in clinical studies in at least 10 patients.

AVOXA EYE DROPS has been studied in patients from babies to adults, including elderly patients.

ln four randomised, double-masked, multicentre, controlled clinical trials in which patients were dosed 3 times a day for 4 days, moxifloxacin produced clinical cures in 80 % to 94 % of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 78 % to 97 %.

ln paediatric patients from birth to one month of age, moxifloxacin produced clinical cure in 80 % of patients with bacterial conjunctivitis. The microbiological success rate for the eradication of the baseline pathogens was 92 %.

In a randomised, double-masked, multicentre, controlled clinical trial in which patients were dosed twice a day for 3 days, moxifloxacin produced clinical cure in 74 % of patients treated for bacterial conjunctivitis. Microbiological success rate for the eradication of the baseline pathogens was 81 %.

Paediatric population

ln paediatric patients from birth to one month of age, moxifloxacin produced clinical cure in 80 % of patients with bacterial conjunctivitis. The microbiological success rate for the eradication of the baseline pathogens was 92 %.

5.2 Pharmacokinetic properties

Following topical ocular administration of AVOXA EYE DROPS, 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 AVOXA EYE DROPS 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 alter well-tolerated therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated 10 be 13 hours.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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 following up to 38 weeks of oral dosing at 500 mg /kg /day.

Moxifloxacin was not mutagenic in four bacterial strains used in the Ames *Salmonella* reversion assay. 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. Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg /kg /day, approximately 21,700 times the highest recommended total daily human ophthalmic dose.

Teratogenic Effects:

Moxifloxacin was not teratogenic when: administered to pregnant rats during organogenesis at oral doses as high as 500 mg /kg /day (approximately 21,700 times he highest recommended total daily human ophthalmic dose); however, decreased foetal body weights and slightly delayed foetal

skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg /kg /day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller foetuses was observed at 100 mg /kg /day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid

1M hydrochloric acid solution

Sodium chloride

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before first opening: 36 months

After first opening: 28 days

6.4 Special precautions for storage

Store at or below 25 ºC.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

AVOXA EYE DROPS is packaged in 5 mL PE bottles sealed with droppers and closed with PE tamper-evident screw caps and packed into cardboard cartons.

Pack size: 1 bottle.

Austell Pharmaceuticals (Pty) Ltd, 540202, Avoxa Eye Drops, 0,5 %

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

54/15.1/0202

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 May 2023

10. DATE OF REVISION OF THE TEXT