Professional Information for Medicines for Human Use

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZOXAN Eye Drops 0, 3 % *w/v*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zoxan Eye Drops contains ciprofloxacin hydrochloride equivalent to 0, 3 % w/v ciprofloxacin)

Preservative: Benzalkonium Chloride NF 0, 006 % *w/v*

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Zoxan Eye drops: Clear colourless solution. Practically free from particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ZOXAN Eye drops are indicated for the treatment of corneal ulceration and conjunctivitis caused by susceptible strains of bacteria.

Appropriate monitoring of bacterial response to topical antibacterial therapy should accompany the use of ZOXAN Eye Drops.

4.2. Posology and method of administration

The recommended dosage regimens for adults and children over the age of two years are as follows:

Corneal ulcers or abscesses:

ZOXAN Eye Drops: On the first day, instil two drops into the affected eye every 15 minutes for the first six hours and then two drops into the affected eye every 30 minutes for the remainder of the day. On the second day, instil two drops in the affected eye hourly. On the third through the fourteenth day, instil two drops into the affected eye every four hours. If the patient needs to be treated longer than 14 days, the dosing regimen is at the discretion of the physician.

Bacterial conjunctivitis:

ZOXAN Eye Drops: Instil one or two drops into the conjunctival sac(s) every two hours while awake for two days, then one or two drops every four hours while awake until the bacterial infection is resolved.

Method of administration:

For ocular use.

4.3 Contraindications

- Hypersensitivity to ciprofloxacin or any components of this medication.
- Hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

4.4 Special warnings and precautions for use

- Zoxan Eye Drops should be discontinued at the first appearance of a skin rash or any other sign of a hypersensitivity reaction. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.
- Prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate measures should be initiated. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy and where appropriate, fluorescein staining.
- As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.
- Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and those treated concurrently with corticosteroids. Therefore, treatment with ZOXAN Eye drops should be discontinued at the first sign of tendon inflammation *(see section 4.8).*
- In patients with corneal ulcer and frequent administration of ZOXAN Eye drops, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of ZOXAN Eye drops. The precipitate does not preclude the continued application of ZOXAN Eye drops nor does it adversely affect the clinical course of the recovery process. The onset of the precipitate was within 24 hours to 7 days after starting therapy. Resolution of the precipitate varied from immediately to 13 days after therapy commencing.
- Contact lens wear is not recommended during treatment of an ocular infection. Therefore, patients should be advised not to wear contact lenses during treatment with ZOXAN Eye drops.
- ZOXAN Eye drops contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. In case patients are allowed to wear contact lenses they should be instructed to remove them prior to application of ZOXAN Eye drops and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicines and other forms of interaction

The systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effect of warfarin and its

derivatives and transient increases in serum creatinine have been observed in patients receiving cyclosporin concomitantly.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

Safety in pregnant women has not been established.

Breastfeeding

Safety in pregnant women and breastfeeding mothers has not been established.

Fertility

Studies have not been performed in humans to evaluate the effect of topical administration of ciprofloxacin on fertility.

4.7 Effects on ability to drive and use machines

ZOXAN Eye drops can cause blurred vison or other visual disturbances (*see section 4.8* Undesirable effects) and may have no or negligible influence or effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

In clinical trials with Ciprofloxacin Ophthalmic Solution, the following treatment-related signs and symptoms have been reported:

a. Summary of safety profile

The following adverse reactions have been reported during clinical trials with Ciprofloxacin Ophthalmic Solution, and are classified according to the subsequent convention:

Frequent (≥ 1/10), (≥ 1/100 to <1/10)

Less frequent (≥ 1/1,000 to <1/100), (≥ 1/10,000 to <1/1,000), (<1/10,000).

Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

b. Tabulated list of adverse reactions

Body System	**Undesirable effect**	
	Frequent	***Less frequent***
Immune system disorders		hypersensitivity
Nervous system disorders		dizziness, headache
Eye disorders	white precipitate and, ocular discomfort	Keratopathy, punctate keratitis, corneal infiltrates, photophobia,

	(stinging and burning may occur upon application), ocular hyperaemia	visual acuity reduced, eyelid oedema, blurred vision, eye pain, eye swelling, pruritus (itching), increased tearing, eye discharge, eyelid margin crusting, crystals/scales, conjunctival oedema, erythema of eyelid, Ocular toxicity, keratitis, conjunctivitis, corneal epithelium defect, diplopia, hypoaesthesia eye, asthenopia, eye irritation, eye inflammation, hordeolum
Ear and labyrinth disorders		ear pain
Respiratory, thoracic and mediastinal disorders		paranasal sinus hypersecretion, rhinitis.
Gastrointestinal disorders	taste perversion (metallic taste)	nausea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders		dermatitis

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

Body System	**Undesirable effect**
Musculoskeletal and connective tissue disorders	tendon disorder

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 Reactions Reporting Form', Found under SAHPRA**"s publications:
https://www/sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see *section 4.8*).
A topical ocular overdose may be flushed from the eye(s) with lukewarm tap water.
Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Other Anti-infective.
ATC Code: S01A X13.

Mechanism of action

Ciprofloxacin is a broad spectrum water soluble fluoroquinolone antibacterial. It has cidal and inhibitory activity against bacteria which result from an interference with the DNA gyrase, an enzyme needed by the bacterium for the synthesis of DNA. Thus, the vital information from the bacterial chromosomes cannot be transcribed any longer, which causes a breakdown in the bacterial metabolism. Ciprofloxacin has an *in vitro* activity against a wide range of Gram-negative microorganisms.

Mechanism of Resistance

Fluoroquinolone resistance, particularly ciprofloxacin, requires significant genetic changes in one or more of five major bacterial mechanisms: a) enzymes for DNA synthesis, b) protecting proteins,

c) cell permeability, d) drug efflux, or e) plasmid-mediated aminoglycoside 6'-N-acetyltransferase, AAC (6')-Ib.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim, and chloramphenicol. Therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin**.**

Breakpoints:

There are no official topical ocular breakpoints for ciprofloxacin and although systemic breakpoints have been used, their relevance to topical therapy is doubtful. The EUCAST clinical MIC breakpoints used for this antibiotic are the following:

Staphylococcus species S≤1mg/l, R≥1mg/l

Streptococcus pneumoniae S≤0.125mg/1, R≥2mg/l

Haemophilus influenzae S≤0.5mg/l, R≥0.5mg/l

Moraxella catarrhalis S≤0.5mg/l, R≥ 0.5mg/l

Pseudomonas aeruginosa S≤0.5mg/l, R≥ 1 mg/l

Inherently resistant organisms
Aerobic Gram-positive micro-organisms:
Corynebacterium jeikium
Aerobic Gram-negative micro-organisms:
None
Other micro-organisms:
None

5.2 Pharmacokinetic properties

Ciprofloxacin is absorbed systemically after topical ocular administration. The maximum reported plasma concentration of ciprofloxacin was less than 5 ng/ml (some 450-folds less than levels observed following simple 250 mg oral administration) and the mean plasma concentration was less than 2.5 ng/ml

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium Edetate
Mannitol (Perlitol SD 200)
Sodium acetate (anhydrous)
Glacial acetic acid
Sodium hydroxide
Hydrochloric acid
Water for Injection

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Proposed shelf-life for unopened vial: 24 months.

Proposed shelf-life for opened vial: 30 days

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Discard product 30 days after opening.

6.5 Nature and contents of container

ZOXAN Eye drops– Clear, Colourless solution, practically free from particles. It is available in 5ml/10 ml labelled LDPE bottle closed with a white opaque HIPS spike cap packed in a carton with pack insert.

6.6 Special precautions for Disposal

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

FDC SA (PTY) LTD
Unit J3, Willows Office Park
Farm Road, The Willows, Pretoria East,
Pretoria, 0081, South Africa.

8 REGISTRATION NUMBER(S)

A40/15.1/0091

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

RENEWAL DATE: 24/05/2021

10 DATE OF REVISION OF TEXT

14-06-2023