SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

ZOXAN Eye / Ear Drops (Ciprofloxacin Ophthalmic Solution USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciprofloxacin.....0.3 % w/v
(As Ciprofloxacin Hydrochloride)
Benzalkonium Chloride ..... 0.01 % w/v
(As preservative)
Aqueous vehicle .....q.s

3. PHARMACEUTICAL FORM

Ophthalmic Solution

Description

A clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOXAN Eye / Ear Drops is indicated for the treatment of corneal ulcers and superficial infections of the eye and adnexa caused by susceptible strains of bacteria in adults and children.

4.2 Posology and method of administration

Topical ocular instillation.

Adults and children above 1 year of age:

Corneal Ulcers:

Zoxan Eye / Ear Drops must be administered in the following intervals, even during night time:

- On the first day, instil 2 drops into the affected eye every 15 minutes for the first six hoursand then 2 drops into the affected eye every 30 minutes for the remainder of the day.
- On the second day, instil 2 drops in the affected eye hourly.
- On the third through the fourteenth day, place two drops in the affected eye every 4 hours.If the patient needs to be treated longer than 14 days, the dosing regimen is at thediscretion of the attending physician.

Superficial Ocular Infection:

Zoxan Eye / Ear Drops to be administered as follows:

- The usual dose is one or two drops in the affected eye(s) four times a day.
- In severeinfections, the dosage for the first two days may be one or two drops every two hoursduring waking hours.

For either indication a maximum duration of therapy of 21 days is recommended.
The dosage in children above the age of 1 year is the same as for adults.

Paediatric Population

In children below 1 year, use this product with caution and dosage to be administered as recommended by the physician.

Method of Administration

- For ocular use only.
- Not for injection.
- Do not touch tip of the vial to finger or to eye(s)/eyelids or to any other surface since this may contaminate the solution.
- If eye irritation occurs, discontinue the use and consult the Physician.
- Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.
- If more than one topical ophthalmic medicinal product is being used, the medicinal products should be instilled 5 to 15 minutes apart. Eye ointments should be administered last.
- Use the solution within one month after opening the vial.

4.3 Contraindications

Zoxan Eye / Ear Drops is contraindicated in patient with known hypersensitivity to the ciprofloxacin or to any other quinolone or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Bacterial Resistance: When using ciprofloxacin eye drops one should take into account the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Hypersensitivity: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systematically administered quinolones. 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 acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated. This product should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Superinfection: As with all antibacterial preparations prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.

Tendinopathy: 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.

Benzalkonium Chloride (BKC) as Preservative: Benzalkonium chloride is used as preservative in this product which has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. This medicinal product should be used with caution in dry eye patients and in patients where the cornea may be compromised.

From the limited data available, there is no difference in the adverse event profile in children compared to adults. However, eyes in children generally show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

Contact Lenses: Contact lenses may absorb benzalkonium chloride and these should be removed before instilling this eye drops but may be reinserted after 15 minutes.

In patients with corneal ulcer and frequent administration of ciprofloxacin eye drops, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of product. The precipitate does not preclude the continued application of the 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.

Paediatric Population
The clinical experience in children less than one year old, particularly in neonates is very limited. The use of ciprofloxacin eye drops in neonates with ophthalmia neonatorum of gonococcal or chalamydial origin is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. Given the low systemic concentration of ciprofloxacin following topical ocular administration of the product, drug interactions are unlikely to occur.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
There are no adequate data from the use of Zoxan Eye / Ear Drop in pregnant woman. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. Systemic exposure to ciprofloxacin after topical use is expected to be low.
As a precautionary measure, it is preferable to avoid the use of Zoxan during pregnancy, unless the therapeutic benefit is expected to outweigh the potential risk to the fetus.

Breast Feeding
Orally administered ciprofloxacin is excreted in the human milk. It is unknown whether ciprofloxacin is excreted in human breast milk following topical ocular or otic administration. A risk to the suckling child cannot be excluded. Therefore, caution should be exercised when Zoxan Eye / Ear Drop is administered to nursing women.

Fertility
Studies have not been performed in humans to evaluate the effect of topical administration of ciprofloxacin on fertility. Oral administration in animals does not indicate direct harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

This product has no or negligible influence on the ability to drive or use machines.
Temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If transient blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

In clinical trials, the most frequently reported adverse drug reactions were ocular discomfort, dysgeusia and corneal deposits occurring approximately in 6%, 3% and 3% of patients respectively.

Tabulated summary of adverse reactions
The adverse reactions listed below are classified according to the following convention: 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), or not known (cannot be estimated from the available data). Within each

frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience.

The following undesirable effects were reported in association with the ophthalmic use of Zoxan:

System Organ Classification	**MEdDRA Preferrred Term (v 15.1)**
Immune System disorders	Rare: hypersensitivity
Nervous system disorders	Uncommon: headache Rare: dizziness
Eye disorders	Common: corneal deposits, ocular discomfort, ocular hyperaemia Uncommon: keratopathy, punctate keratitis, corneal infiltrates, photophobia, visual acuity reduced, eyelid oedema, blurred vision, eye pain, dry eye, eye swelling, eye pruritus, lacrimation increased, eye discharge, eyelid margin crusting, eyelid exfoliation, conjunctival oedema, erythema of eyelid Rare: ocular toxicity, keratitis, conjunctivitis, corneal epithelium defect, diplopia, hypoaesthesia eye, asthenopia, eye irritation, eye inflammation, hordeolum
Ear and Labyrinth disorders	Rare: ear pain
Respiratory, thoracic and mediastinal disorders	Rare: paranasal sinus hypersecretion, rhinitis
Gastrintestinal disorders	Common: dysgeusia Uncommon: nausea Rare: diarrhoea, abdominal pain
Skin and subcutenous tissue disorders	Rare: dermatitis
Musculoskeletal and connective tissue disorders	Not known: tendon disorder

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, 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.
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 fluoroquinolones indicate that the risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including the Achilles tendon. To date, clinical and post marketing data have not demonstrated a clear association between Zoxan and musculoskeletal and connective tissue adverse reactions.
In isolated cases blurred vision, decreased visual acuity and medication residue have been observed with ophthalmic ciprofloxacin.
Moderate to severe phototoxicity has been observed in patients treated with systemic quinolones. Nevertheless, phototoxic reactions to ciprofloxacin are uncommon.

Paediatric population
Safety and effectiveness of Zoxan 3mg/ml eye drops were determined in 230 children between the ages of 0 and 12 years of age. No serious adverse drug reaction was reported in this group of patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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4.9 Overdose
A topical overdose of Zoxan Eye / Ear Drops may be rinsed out from the eye(s) with lukewarm tap water. Due to the characteristics of this preparation no toxic effects are to be expected with an ocular overdose of this product, or in the event of accidental ingestion of the contents of one bottle.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Ophthalmologicals, Other Anti-infective.
ATC code: S01AX13

Mechanism of action
This medicinal product contains ciprofloxacin, a broad-spectrum anti-infective agent that belongs to the fluoroquinolones group. The cidal and inhibitory activity of ciprofloxacin against bacteria results 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 which causes a breakdown of the bacterial metabolism and thereby death of bacterial cell.

Bacterial 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.

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 the agent in at least some types of infections is questionable. The presentation below lists bacterial species recovered from external ocular infections of the eye.

Pharmacodynamic Effects / Microbiology

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

Commonly susceptible species

Aerobic Gram-positive microorganisms

- *Corynebacterium accolens*
- *Corynebacterium auris*
- *Corynebacterium propinquum*
- *Corynebacterium psudodiphtheriticum*
- *Corynebacterium striatum*
- *Staphylococcus aureus* (methicillin susceptible - MSSA)
- *Staphylococcus capitis*
- *Staphylococcus epidermidis* (methicillin susceptible - MSSE)
- *Staphylococcus hominis*
- *Staphylococcus saprophyticus*
- *Staphylococcus warneri*
- *Streptococcus pneumoniae*
- *Streptococcus viridans* Group

Aerobic Gram-negative microorganisms

- *Acinetobacter species*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Pseudomonas* aeruginosa
- *Serratia marcescens*

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms:

- *Staphylococcus aureus* (methicillin resistant - MRSA)
- *Staphylococcus epidermidis* (methicillin resistant - MRSE)
- *Staphylococcus lugdunensis*

Inherently resistant organisms

Aerobic Gram-positive micro-organisms:

- *Corynebacterium jeikium*

5.2 Pharmacokinetic properties

Ciprofloxacin ophthalmic solution is rapidly absorbed into the eye following topical ocular administration. Systemic levels are low following topical administration. Plasma levels of ciprofloxacin in human subjects following 2 drops of 0.3% ciprofloxacin solution every 2 hours for two days and then every four hours for 5 days ranged from non-quantifiable (<1.0 ng/mL) to 4.7 ng/mL. The mean peak ciprofloxacin plasma level obtained in this study is approximately 450-fold less than that seen following a single oral dose of 250 mg ciprofloxacin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical developmental toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium Edetate, Sodium Chlrodie, Benzalkonium Chloride, Disodium Hydrogen Phosphate Dodecahydrate, Sodium Hydroxide, Hydrochloric Acid, Water for Injection

6.2 Incompatibilities

Incompatible with alkaline solutions.

6.3 Shelf life:

24 months

6.4 Special precautions for storage

Store at a temperature not exceeding 25°C.
Protect from light.

6.5 Nature and contents of container

5 mL solution filled in 5 mL labelled LDPE vial provided with spike HIPS cap and packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Name: FDC Limited
Address: B- 8, MIDC Industrial Area, Waluj, Aurangabad- 431 136, Maharashtra
Phone: 0240- 2554407/ 2554967
Fax: 0250 - 2554299
E-mail: sachin.lawadkar@fdcindia.com

8. MARKETING AUTHORISATION NUMBER(S)

Certificate no; 04967/07160/REN/2019

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Feb 04, 2020

10. DATE OF REVISION OF THE TEXT

August 2023