CIPLOX Eye/Ear Drops (Ciprofloxacin)

Qualitative and Quantitative Composition

CIPLOX Eye/Ear Drops

Ciprofloxacin .....0.3% w/v

Benzalkonium Chloride, NF .....0.01% w/v
(Preservative)
Sterile aqueous vehicle ..... q.s.

Dosage Form(s) and Strength(s)

Ciprofloxacin (0.3% w/v) Eye/ear drops

Clinical Particulars

Therapeutic Indications

In Adults and Children (age ≥1 year)

Ciprofloxacin eye/ear drops is indicated for the treatment of external ocular infection of the eye caused by susceptible strains of bacteria.

Ciprofloxacin eye/ear drops are indicated for the topical treatment of Chronic Suppurative otitis media, external otitis, malignant otitis externa and peri operatively in chronic otitis media.

Posology and Method of Administration

External Ocular Infection

Adults and Children (age ≥1 year)***:*** The usual dose is one or two drops in the affected eye(s) four times a day. In severe infections, the dosage for the first 2 days may be one or two drops every 2 hours during waking hours.

A maximum duration of therapy of 21 days is recommended.

Ears Infections

Adults and Children (age ≥1 year)***:*** For all infections, two to three drops every 2–3 hours initially, reducing the frequency of the instillation with control of infection.

Contraindications

A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use.

A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

Special Warnings and Precautions for Use

General

NOT FOR INJECTION INTO THE EYE. FOR TOPICAL USE ONLY.

The clinical experience in children less than one year old, particularly in neonates is very limited. The use of **CIPLOX Eye/Ear 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.

When using **CIPLOX Eye/Ear Drops** one should take into account the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.
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. Only a few patients had a history of hypersensitivity reactions.

Serious acute 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.

CIPLOX Eye/Ear Drops should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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.

Remove contact lenses before using. During therapy, soft contact lenses should not be worn.

As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, appropriate therapy 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.

In clinical studies of patients with bacterial corneal ulcers, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In 1 patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1-8 days (in 7 days if treated within the first 24-72 hours). In 5 patients, resolution was noted in 10-13 days. In 9 patients, exact resolution days were unavailable; however, at follow-up examinations, 18–44 days after onset of the event, complete resolution of the precipitate was noted. In 3 patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome.

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 ciprofloxacin eye/ear drops should be discontinued at the first sign of tendon inflammation.

During therapy, soft contact lenses should not be worn.

CIPLOX Eye/Ear Drops contain benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses.

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 **CIPLOX Eye/Ear Drops**.

Drugs Interactions

Specific drug interaction studies have not been conducted with ciprofloxacin eye/ear drops. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Use in Special Populations

Pregnant Women

Pregnancy Category C

Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human oral dose and have revealed no evidence of impaired fertility or harm to the foetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are no adequate and well-controlled studies in pregnant women.

There are no adequate and well-controlled studies in pregnant women. **CIPLOX Eye/Ear Drops** should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactating Women

It is not known whether topically applied ciprofloxacin is excreted in human milk; however, it is known that orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose. Caution should be exercised when **CIPLOX Eye/Ear Drops** are administered to a nursing mother.

Paediatric Patients

Safety and effectiveness of ciprofloxacin eye/ear drops have been established in all ages.

Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the administered dosage form has any effect on the weight-bearing joints.

Geriatric Patients

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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.

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.

Undesirable Effects

Because clinical studies are conducted under widely varying conditions, adverse drug reaction rates observed in the clinical studies of a drug cannot be directly compared with rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

The most frequently reported drug-related adverse reaction was local burning and discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients. Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperaemia, and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid oedema, tearing, photophobia, corneal infiltrates, nausea and decreased vision. Hypersensitivity reactions cannot be excluded.

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 postmarketing experience.

The following undesirable effects were reported in association with the use of ciprofloxacin eye/ear drops:

System Organ Classification	**MedDRA Preferred Term (v. 15.1)**
Infections and infestations	*Rare:* hordeolum, rhinitis
Immune system disorders	*Rare:* hypersensitivity
Nervous system disorders	*Common:* dysgeusia *Uncommon:* headache *Rare:* dizziness

Eye disorders	*Common:* corneal deposits, ocular discomfort, ocular hyperaemia *Uncommon:* keratopathy, corneal infiltrates, corneal staining, photophobia, visual acuity reduced, eyelid oedema, blurred vision, eye pain, dry eye, eye swelling, eye pruritus, foreign body sensation in eyes, lacrimation increased, eye discharge, eyelid margin crusting, eyelid exfoliation, conjunctival oedema, erythema of eyelid *Rare:* ocular toxicity, punctate keratitis, keratitis, conjunctivitis, corneal disorder, corneal epithelium defect, diplopia, hypoaesthesia eye, asthenopia, eye irritation, eye inflammation, conjunctival hyperaemia
Ear and labyrinth disorders	*Rare:* ear pain
Respiratory, thoracic and mediastinal disorders	*Rare:* paranasal sinus hypersecretion, rhinitis.
Gastrointestinal disorders	*Uncommon:* nausea *Rare:* diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	*Rare:* dermatitis
General disorders and administration site conditions	*Rare:* drug intolerance
Musculoskeletal and connective tissue disorders	*Not known: tendon disorder*
Investigations	*Rare:* laboratory test abnormal

Description of Selected Adverse Events

With locally applied fluoroquinolones(generalised) 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.

In patients with corneal ulcers and frequent administration of the drug, white precipitates have been seen with locally applied fluoroquinolones; (generalised) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely.

Ruptures of the shoulder, hand, Achilles’ tendon, or other tendons that required surgical repair or

resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and postmarketing 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 postmarketing data have not demonstrated a clear association between ciprofloxacin eye/ear drops and musculoskeletal and connective tissue adverse reactions.

In isolated cases, blurred vision, decreased visual acuity and medication residue have been observed with ophthalmic ciprofloxacin.

Safety and effectiveness of ciprofloxacin eye/ear drops were determined in 230 children between the ages of 0 and 12 years. No serious adverse drug reaction was reported in this group of patients.

Systemic Absorption of fluoroquinolones has been reported to cause following adverse effects:

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below;

- Disturbances in attention
- Disorientation
- Agitation
- Nervousness
- Memory impairment
- Serious disturbances in mental abilities called delirium

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

A topical overdose of ciprofloxacin eye drops may be flushed 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.

Pharmacological Properties

Mechanism of Action

The bactericidal action of ciprofloxacin results from inhibition of the enzyme, DNA gyrase, which is required for the synthesis of bacterial DNA.

Pharmacodynamic Properties

Pharmacotherapeutic Group – Ophthalmologicals, Other Anti-infectives.

ATC Code: S01A X13.

CIPLOX Eye/Ear Drops contain the fluoroquinolone, ciprofloxacin. The bactericidal 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. Ciprofloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative bacteria.

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'--
-acetyltransferase, AAC (6')-Ib.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulphonamides, 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 as follows:

Staphylococcus species	S ≤1 mg/l, R ≥1 mg/l
Streptococcus pneumoniae	S ≤0.125 mg/l, R ≥2 mg/l
Haemophilus influenzae	S ≤0.5 mg/l, R ≥0.5 mg/l
Moraxella catarrhalis	S ≤0.5 mg/l, R ≥0.5 mg/l
Pseudomonas aeruginosa	S ≤0.5 mg/l, R ≥1 mg/l

Susceptibility 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.

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 MICROORGANISMS

Staphylococcus aureus (methicillin-resistant – MRSA)

Staphylococcus epidermidis (methicillin-resistant – MRSE)

Staphylococcus lugdunensis

AEROBIC GRAM-NEGATIVE MICROORGANISMS

None

OTHER MICROORGANISMS

None

Inherently Resistant Organisms

AEROBIC GRAM-POSITIVE MICROORGANISMS

Corynebacterium jeikium

AEROBIC GRAM-NEGATIVE MICROORGANISMS

None

OTHER MICROORGANISMS

None

Pharmacokinetic Properties

Ciprofloxacin in **CIPLOX Eye/Ear Drops** 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 two drops of 0.3% ciprofloxacin solution every 2 hours for 2 days and then every 4 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. The systemic pharmacokinetic properties of ciprofloxacin have been well studied. Ciprofloxacin widely distributes to tissues of the body. The apparent volume of distribution at steady state is 1.7–5.0 l/kg. Serum protein-binding is 20–40%. The half-life of ciprofloxacin in serum is 3–5 hours. Both ciprofloxacin and its four primary metabolites are excreted in urine and faeces. Renal clearance accounts for approximately two-thirds of the total serum clearance with biliary and faecal routes accounting for the remaining percentages. In patients with impaired renal function, the elimination half-life of ciprofloxacin is only moderately increased due to extra-renal routes of elimination. Similarly, in patients with severely reduced liver function the elimination half-life is only slightly longer.

There are no pharmacokinetic data available with respect to use in children.

Non-Clinical Properties

Animal Toxicology or Pharmacology

After topical application of ciprofloxacin 0.3%, (one drop every 30 minutes for a total of six doses), the concentration of ciprofloxacin achieved in the aqueous humour of rabbits when the corneal epithelium was intact was 4.8 µg/mL; when debrided, it was 12.9 µg/mL.

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.

Description

Ciprofloxacin eye/ear drops, USP, is a synthetic, sterile, multiple dose, antimicrobial for topical ophthalmic and otic use. Ciprofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Pharmaceutical Particulars

Incompatibilities

Incompatible with alkaline solutions.

Shelf-Life

As on the pack.

Packaging Information

Ciplox Eye/Ear Drops.....Vial of 10 ml

Storage and Handling Instructions

Protect from light.

Patient Counselling Information

What is CIPLOX Eye/Ear Drops?

CIPLOX Eye/Ear Drops belongs to a group of medicines known as quinolone antibiotics.

Do not take if you have allergy to CIPLOX Eye/Ear Drops?

Do not use **CIPLOX Eye/Ear Drops** If you are allergic (hypersensitive) to ciprofloxacin or any other quinolone antibiotic or to any of the other key ingredients

Before you take this medicine, tell your HCP about other medication.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you are using more than one type of eye medicine, the medicines must be used at least 5 minutes apart. Eye ointments should be used last.

How should I use CIPLOX Eye/Ear Drops?

Always use **CIPLOX Eye/Ear Drops** exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

What are the possible side effects?

Like all medicines, **CIPLOX Eye/Ear Drops** can cause side effects, although not everybody gets them.

You may experience some or all the following effects in your eye(s):

Common (1 to 10 users in 100)

- White deposits on the eye surface (cornea)
- discomfort (stinging or burning, gritty feeling in the eye, irritation)
- redness

Uncommon (1 to 10 users in 1,000)

- Damage to the eye surface (cornea)
- Sensitivity to light
- Blurred vision
- Swelling of the eye or eyelid, pain
- Dry eye
- Itchiness

- Eye discharge
- Eyelid crusting
- Eyelids scales
- Eyelid redness
- Poor vision
- Watery eyes
- Red eyes

Rare (1 to 10 users in 10,000)

- Damage of the eye
- Inflammation
- Double vision
- Decreased eye sensation
- Tired eyes, stye

If you notice white particles in your eyes, continue to use **CIPLOX Eye/Ear Drops** but tell your doctor immediately.

You may also experience effects in other areas of your body such as the following:

Common: bad taste.

Uncommon: headache, nausea.

Rare: hypersensitivity, dizziness, ear pain, inflammation inside the nose, nasal sinus discharge, diarrhoea, abdominal pain, skin inflammation, tendon disorder.

If you experience an allergic reaction, stop using **CIPLOX Eye/Ear Drops** and tell your doctor.

How should I store CIPLOX Eye/Ear Drops?

- Keep out of the reach and sight of children.
- Do not store above 25°C.
- Do not refrigerate or freeze.
- Keep the bottle tightly closed.
- Do not use the drops after the expiry date (marked 'EXP') on the bottle and the carton. The expiry date refers to the last day of that month

General information about the safe and effective use of CIPLOX Eye/Ear Drops.

CIPLOX Eye/Ear Drops belongs to a group of medicines known as quinolone antibiotics. It is used for the treatment of external ocular Infection of the eye and topical treatment of otitis media, external otitis, malignant otitis externa and peri operatively in chronic otitis media.

Ask your doctor for advice and take special care.

- Use **CIPLOX Eye/Ear Drops** only in your eyes and ears.
- Only use **CIPLOX Eye/Ear Drops** in children younger than 1 year if prescribed by your doctor.
- As with any antibiotic, use of **CIPLOX Eye/Ear Drops** for a long time may lead to other infections. If your symptoms get worse or suddenly return tell your doctor. You may become more susceptible to other infections with the use of this medicine, especially after prolonged use.

If you notice the first signs of a skin rash or any other allergic reaction, including hives, itching and breathing problems stop treatment and immediately contact your doctor. If you have a serious allergic reaction, then you may need emergency treatment.

- If you feel pain, swelling or inflammation while or shortly after taking this medicine, stop treatment and contact your doctor.
- If you are elderly or if you are taking medicines called 'corticosteroids' used to treat conditions such as pain and inflammation, asthma or skin problems, then you have a higher risk of getting tendon problems during treatment with **CIPLOX Eye/Ear Drops**. If you experience any inflammation or inflammatory condition, stop treatment and immediately consult your doctor.

Pregnancy and Breastfeeding

If you are pregnant or might get pregnant, or if you are breastfeeding a baby, talk to your doctor before you use **CIPLOX Eye/Ear Drops**.

Driving and Using Machines

If your sight is temporarily blurred or affected in any way following use of **CIPLOX Eye/Ear Drops** you should not drive or operate machinery until your vision is clear again.

Important Information if you Wear Contact Lenses

There is a preservative in **CIPLOX Eye/Ear Drops** (benzalkonium chloride) that may cause eye irritation and can discolour soft contact lenses. Do not wear contact lenses (hard or soft) during treatment with **CIPLOX Eye/Ear Drops**. If you do continue to wear your lenses, you must remove them before using **CIPLOX Eye/Ear Drops** and wait at least 15 minutes after use before putting your lenses back in.

What are the ingredients in CIPLOX Eye/Ear Drops?

CIPLOX Eye/Ear Drops contain Ciprofloxacin 0.3% and Benzalkonium Chloride, NF 0.01% (Preservative) with Sterile aqueous vehicle.

Any other information

None.

Details of the Manufacturer

Mfd. by CIPLA LTD.

C-116 B, Road No.,

Vishwakarma Industrial Area,

Jaipur 302 013.

At: SP-91, Phase III,

Bhiwandi 301 019

Details of Permission or Licence Number with Date

M.L. Raj – 1704-A

Date of Revision

13th September 2019