For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Ciprofloxacin Eye Drops IP
(Brand Name: CEBRAN® Eye Drops)

WARNING
Fluoroquinolones, including ciprofloxacin have been associated with disabling and potentially irreversible serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbation of myasthenia gravis.
Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions.
Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.

2. Qualitative and Quantitative Composition

Composition
Ciprofloxacin Hydrochloride IP equivalent to Ciprofloxacin ……. 0.3% w/v.
Benzalkonium Chloride Solution IP ……... 0.02% w/v.
(as preservative)
Water for Injections IP ……. q.s.

3. Dosage Form and Strength

Dosage Form: Eye drops / Ophthalmic solution.
Dosage Strength: Ciprofloxacin 0.3% w/v as an ophthalmic solution.

4. Clinical Particulars

4.1 Therapeutic Indication

CEEBRAN Eye Drops are indicated for the treatment of corneal ulcers and conjunctivitis caused by susceptible strains of bacteria.

4.2Posology and Method of Administration

For topical ocular use only.
Ciprofloxacin ophthalmic solution to be administered as per following dosing schedule in adults and children above 1 year of age.

Corneal Ulcers

The recommended dosage regimen is:

- On the first day: Instill 2 drops into the affected eye every 15 minutes for the first 6 hours, then 2 drops into the affected eye every 30 minutes for rest of the day.
- On the second day: Instill 2 drops in the affected eye hourly.
- On the third through the fourteenth day: Instill 2 drops in the affected eye every 4 hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.

Bacterial Conjunctivitis
The recommended dosage regimen is:

- For initial 2 days: Instill 1 or 2 drops into the conjunctival sac(s) every 2 hours while awake.
- For the next 5 days: Instill 1 or 2 drops every 4 hours while awake.

For either indication a maximum recommended duration of therapy is 21 days.
Or, as prescribed by the physician.

4.3Contraindications

CEBRAN Eye Drops are contraindicated in patients with known or suspected hypersensitivity to ciprofloxacin or to any other quinolone or to any excipient of the formulation.

4.4Special Warnings and Precautions for Use

General Precautions

- For external use only.
- Not for injection.
- After opening, do not touch the vial tip or any surface as this may contaminate the solution.
- If irritation persists or increases discontinue use and consult the physician.
- Remove contact lenses before using this product. CEBRAN Eye Drops contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses they should be instructed to remove them prior to application of drops and wait at least 15 minutes before reinsertion.

Hypersensitivity: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction. Some reactions have been accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, 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.

As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

The clinical experience in children less than one year old, particularly in neonates, is very limited. The use of CEBRAN 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.

When using CEBRAN Eye Drops one should take into account the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

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 CEBRAN Eye Drops should be discontinued at the first sign of tendon inflammation.

In patients with corneal ulcer and frequent administration of CEBRAN Eye Drops, white topical ocular precipitates (medication residue) have been observed which resolved after continued application. The precipitate does not preclude the continued use of ciprofloxacin nor does it adversely affect the clinical course or visual outcome. 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.

Effects on ability to drive and use machines: Ciprofloxacin ophthalmic solution 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.

4.5Drug Interactions

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

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.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category C. Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral dose and has revealed no evidence of impaired fertility

or harm to the fetus 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. However, there are no adequate and well controlled studies in pregnant women. CEBRAN Eye Drops should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactating Women

It is not known whether topical ocular administration of 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 CEBRAN Eye Drops are administered to a nursing mother.

Paediatric Patients

The dosage in children above the age of 1 year is the same as for adults. Safety and effectiveness in pediatric patients below the age of 1 year have not been established. 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 ophthalmic 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. Elderly patients may be given the same dose as recommended for adults.

4.7Effect on Ability to Drive and Use Machines

CEBRAN Eye Drops 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.

4.8Undesirable Effects

In clinical trials, the most frequently reported adverse drug reactions were local burning, ocular discomfort, dysgeusia, and corneal deposits. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates (medication residue) were seen in approximately 17% of patients. Other reactions occurring in less than 10% of patients included eyelid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, decreased visual acuity, nausea, and blurred vision.

With locally applied fluoroquinolones, rash (generalized), dermatitis exfoliative, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and urticaria may occur. Moderate to severe phototoxicity has been observed in patients treated with systemic quinolones. Nevertheless, phototoxic reactions to ciprofloxacin are uncommon.

4.9Overdose

A topical overdose of ciprofloxacin ophthalmic solution may be rinsed out from the eye(s) with lukewarm tap water. No toxic effects are expected with an ocular overdose or in the event of accidental ingestion of this product.

5. Pharmacological Properties

5.1 Mechanism of Action

Ciprofloxacin, a fluoroquinolone antibacterial agent, is active against a broad spectrum of gram-positive and gram-negative ocular pathogens. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA. Thus, the vital information from the bacterial chromosomes cannot be transcribed which causes a breakdown of the bacterial metabolism and finally, bacterial cell death.

5.2Pharmacodynamic Properties

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections.

Gram-Positive Bacteria

- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus pneumoniae*
- *Streptococcus* (Viridans Group)

Gram-Negative Bacteria

- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Ciprofloxacin has been shown to be active *in vitro* against most strains of the following organisms, however, the clinical significance of these data is unknown:

Gram-Positive Bacteria

- *Enterococcus faecalis* (many strains are only moderately susceptible)
- *Staphylococcus haemolyticus*
- *Staphylococcus hominis*
- *Staphylococcus saprophyticus*
- *Streptococcus pyogenes*

Gram-Negative Bacteria

- *Acinetobacter calcoaceticus subsp. anitratus*
- *Aeromonas caviae*
- *Aeromonas hydrophila*
- *Brucella melitensis*
- *Campylobacter coli*
- *Campylobacter jejuni*
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Edwardsiella tarda*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus ducreyi*
- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Legionella pneumophila*
- *Moraxella (Branhamella) catarrhalis*
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Pasteurella multocida*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Salmonella enteritidis*
- *Salmonella typhi*
- *Shigella sonneii*
- *Shigella flexneri*
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- *Vibrio vulnificus*
- *Yersinia enterocolitica*

Other Organisms

Chlamydia trachomatis (only moderately susceptible) and *Mycobacterium tuberculosis* (only moderately susceptible).

Most strains of *Pseudomonas cepacia* and some strains of *Pseudomonas maltophilia* are resistant to ciprofloxacin same as most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).
There is no known cross-resistance between ciprofloxacin and other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

5.3Pharmacokinetic Properties

Ciprofloxacin 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 2 days and then, every 4 hours for 5 days ranged from < 1.0 ng/ml (non-quantifiable) to 4.7 ng/ml. The mean peak ciprofloxacin plasma level obtained 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 to 5.0 l/kg. Serum protein binding is 20 to 40%. The half-life of ciprofloxacin in serum is 3 to 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a one-month topical ocular study using immature Beagle dogs did not demonstrate any articular lesions.
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.

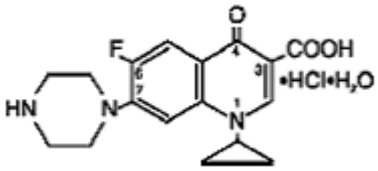
7. Description

CEBRAN Eye Drops are clear colourless to almost colourless solution filled in 10 ml plastic vials.

CEBRAN Eye Drops contain 0.3% of ciprofloxacin for topical ocular use in adults and children above 1 year.

Ciprofloxacin is a synthetic broad spectrum fluoroquinolone antibiotic. Ciprofloxacin hydrochloride is a faintly yellowish to light yellow crystalline substance.

Molecular Weight: 385.8 g/mol.
Molecular Formula: C17H18FN3O3.HCl.H2O
Chemical Name: 1-cyclopropyl-6-fluoro-1,4 dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of CEBRAN Eye Drops contain Borax, Boric Acid, E.D.T.A. Disodium, Sodium Chloride & Glacial Acetic Acid.

8. Pharmaceutical Particulars

8.1 Incompatibilities

Incompatible with alkaline solutions.

8.2Shelf-life

24 Months

8.3Packaging Information

10 ml plastic vial

8.4Storage and Handling Instructions

Store protected from light. Keep out of reach of children.
Discard unused portion of eye drop, if any, after one month of first opening.

9. Patient Counseling Information

Administration Instructions

- Instruct patients/care givers not to use this medicine in larger or smaller amounts or for longer than recommended. Use only the number of drops your doctor has prescribed. Follow all the directions of your Doctor.
- Instruct patients to remove contact lenses before using this eye drops.
- Patients should wash their hands before using eye drops.
- Instruct patients not to touch dropper tip to any surface, as this may contaminate the solution.
- Advice patients to tilt their head back slightly and pull down lower eyelid to create a small pocket. Hold the dropper above the eye with the tip down. Look up and away from the dropper and squeeze out a drop.
- Instruct patients to close eyes for 2 or 3 minutes with head tipped down, without blinking or squinting.
- Instruct patients/care givers to wait at least 10 minutes before using any other eye drops.

10. Details of Manufacturer

Nitin Lifesciences Ltd.
Rampur Road, Paonta Sahib,
Distt. Sirmour, H.P. – 173 025.

11. Details of Permission or License Number with Date

Manufacturing License No.: MB/05/209.Date of Product Permission: 11/09/2015

12.Date of Revision

November 2022.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.