1. NAME OF THE MEDICINAL PRODUCT

CILOXAN®

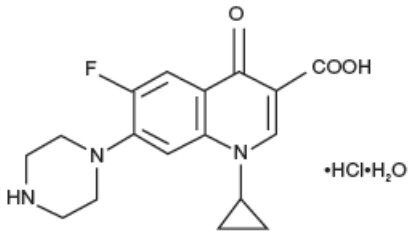
3 mg/g eye ointment (Ciprofloxacin)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of ointment contains 3 mg ciprofloxacin base (equivalent to 3.5 mg ciprofloxacin hydrochloride monohydrate).

For the full list of excipients, see section 6.1.

Ciprofloxacin is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 385.8.
Its empirical formula is $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$ and its chemical structure is as follows:



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.

3. PHARMACEUTICAL FORM

Sterile eye ointment
White to off-white, homogeneous ointment

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CILOXAN® Eye Ointment is a synthetic, sterile, multiple dose, antimicrobial
for topical ophthalmic use. Ciprofloxacin is a fluoroquinolone antibacterial.
CILOXAN Eye Ointment is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the microorganisms listed below:

Gram-Positive :
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus Viridans Group

Gram-Negative:
Haemophilus influenza

4.2 Posology and method of administration

Posology

Apply a 1/2" ointment ribbon into the conjunctival sac 3 times a day on the first 2 days, then apply a 1/2" ointment ribbon 2 times a day for the next 5 days.

Use in elderly
Clinical studies have indicated dosage modifications are not required for the elderly.

Use in children
Safety and effectiveness of CILOXAN Eye Ointment in pediatric patients below the age of two years have not been established.

Use in patients with hepatic or renal impairment
No studies have been performed using ciprofloxacin 3 mg/g eye ointment in patients with kidney or liver problems.

Method of administration
For ocular use.

To prevent contamination of the tube tip and ointment, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the tube tip. Keep the tube tightly closed when not in use.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- hypersensitivity to other quinolones

4.4 Special warnings and precautions for use

- FOR TOPICAL OPHTHALMIC USE ONLY.NOT FOR INJECTION INTO THE EYE.
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose were observed in patients receiving treatment based on systemically administered quinolone. 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. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

- Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management should be administered where clinically indicated.
- As with other antibacterial preparations, prolonged use may lead to overgrowth of non-susceptible bacterial strains or 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.
- Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. Therefore treatment with CILOXAN eye ointment should be discontinued at the first sign of tendon inflammation.
  In patients with corneal ulcer and frequent administration of CILOXAN eye ointment, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of CILOXAN eye ointment. The precipitate does not preclude the continued application of CILOXAN eye ointment, nor does it adversely affect the clinical course of the recovery process.
- Eye Ointments may retard corneal healing and cause visual blurring.
- 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 CILOXAN eye ointment.

4.5 Interaction with other medicinal products and other forms of interaction

Given the low systemic concentration of ciprofloxacin following topical ocular administration of the product, drug interactions are unlikely to occur.

Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

There are no or limited amount of data from the use of CILOXAN eye ointment in pregnant women. Animal studies with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity.

As a precautionary measure, it is preferable to avoid the use of CILOXAN eye ointment during pregnancy.

Breast-feeding :
Ciprofloxacin is excreted in human milk after its oral administration. It is known that orally administered ciprofloxacin is excreted in the milk of lactating rats. It is unknown whether ciprofloxacin is excreted to human milk following topical ocular administration. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from CILOXAN eye ointment therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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.
Although ciprofloxacin and other quinolones may 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.

4.7 Effects on ability to drive and use machines

CILOXAN eye ointment has no or negligible influence on the ability to drive or use machines.

However, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon administration, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile
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 following adverse reactions have been reported during clinical trials and identified from post-marketing surveillance. These are classified according to the subsequent 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; data from post-marketing surveillance). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions**
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, hordeolum, eye irritation, eye inflammation
Ear and labyrinth disorders	*Rare:* ear pain
Respiratory, thoracic and mediastinal disorders	*Rare:* paranasal sinus hypersecretion, rhinitis
Gastrointestinal disorders	*Common:* dysgeusia *Uncommon:* nausea *Rare:* diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	*Rare:* dermatitis
Musculoskeletal and connective tissue disorders	*Not known:* tendon disorder

4.9 Overdose

An ocular overdose of CILOXAN Eye Ointment 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, nor in the event of accidental ingestion of the contents of one tube.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinfectives, fluoroquinolones. ATC code: S01AE03.

Mechanism of Action

CILOXAN eye ointment contains the fluoroquinolone ciprofloxacin. The cidal and inhibitory activity of ciprofloxacin involves inhibition of the α-subunit of bacterial enzyme, DNA gyrase (topoisomerase II) involved in gyrase-mediated DNA supercoiling and DNA synthesis. This process ultimately results in cell death. By targeting DNA gyrase, ciprofloxacin arrests bacterial cell growth and division by stabilizing the DNA-enzyme complex, which temporarily results in bacteriostasis. Subsequently, bacteria attempt but are unable to repair the DNA lesion. DNA ends from the ciprofloxacin-gyrase-DNA complex are eventually liberated creating lethal double-strand DNA breaks. Therefore, ciprofloxacin is bactericidal as well as bacteriostatic. The bactericidal activity of ciprofloxacin and other fluoroquinolones is concentration-dependent. Higher “kill rates” are achieved at peak concentrations. Ciprofloxacin has

been shown to be active against most strains of the following organisms both in vitro and in clinical infections (see section 4.2).

Gram-Positive:

Staphylococcus aureus (including methicillin-susceptible and methicillin- resistant strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus (Viridans Group)

Gram-Negative:

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:

Bacillus species
Corynobacterium species
Enterococcus faecalis (Many strains are only moderately susceptible)
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Streptococcus pyogenes

Gram-Negative:

Acinetobacter caloacetius subsp anitratus
Aeromonas caviae
Aeromonas hydrophilia
Brucella melitensis
Campylobacter coli
Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilius ducreyl
Haemophilius parainfluenza
Klebsiella pneumoniae
Klebsiella oxytoca
Legionella pneumophilia
Moraxella (Branhamella) catarrhalis

Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Pasteurella multocida
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella enteritidis
Salmonella typhi
Shigella sonneli
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 Burkholderia cepacia and some strains of Pseudomonas maltophilia and Stenotrophomonas maltophilia are resistant to ciprofloxacin as are 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).
Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides;
therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. Organisms resistant to ciprofloxacin may be susceptible to beta-lactams or aminoglycosides.

Clinical studies:
In multicenter clinical trials, approximately 75% of the patients with signs and symptoms of bacterial conjunctivitis and positive conjunctival cultures were clinically cured and approximately 80% had presumed pathogens eradicated by the end of treatment (day 7).

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 responses.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim, and chloramphenicol. Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides. Therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. Organisms resistant to ciprofloxacin may be susceptible to beta-lactams or aminoglycosides.

Resistant strains, particularly of MRSA (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Campylobacter jejuni, Neisseria gonorrhoeae, Streptococcus pneumoniae)* have emerged during treatment with ciprofloxacin although there are widely differing patterns of resistance

geographically. Resistance to ciprofloxacin has usually been chromosomally mediated although plasma mediated resistance has recently been noted. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

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 pneumonia	S ≤ 0.125mg/l, R ≥ 2mg/l
Haemophilus influenza	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 ≥ 1mg/l

5.2 Pharmacokinetic properties

Ciprofloxacin Ophthalmic Solution 0.3% is rapidly absorbed into the eye following topical ocular administration. In rabbits, maximal concentrations in most tissues were attained within 0.5 to 2 hours. Systemic levels are low following topical administration.

Plasma levels of ciprofloxacin in human subjects (N=12) following 2 drops of 0.3% ciprofloxacin solution in each eye every 2 hours while awake for two days and then every four hours while awake for an additional 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 (2.6 ± 0.8 ng/ml) is approximately 450-fold less than that seen following a single oral dose of 250 mg ciprofloxacin. Systemic exposure following administration of CILOXAN eye ointment has not been determined.

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 20-40% (4). 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 extrarenal routes of elimination. Similarly, in patients with severely reduced liver function the elimination half-life is only slightly longer.

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

Liquid paraffin, white soft paraffin.

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Store at 2° C to 25° C.

Do not use this medicine after the expiry date which is stated on the packaging.

Keep this medicine out of the sight and reach of children.

6.4 Nature and contents of container

Tube containing 3.5 of ointment.

6.5 Special precautions for disposal

No special requirements.

6.6 Manufacturer

See folding box

(Information Issued: Feb 2013.SINv1)

Novartis Pharma AG, Basel, Switzerland