SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CILOXAN 0.3% w/v eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciprofloxacin 0.3% w/v (as hydrochloride)

Excipients with known effect: One ml of solution contains 0.06mg of benzalkonium chloride

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.
A clear and colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 – 16 years)

CILOXAN is indicated for the treatment of corneal ulcers and superficial infections of the eye and adnexa caused by susceptible strains of bacteria.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults, newborn infants (0-27 days), infants and toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 – 16 years)

Corneal Ulcers:
CILOXAN 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 hours and 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 the discretion of the attending physician.

Superficial Ocular Infection:
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 two days may be one or two drops every two hours during 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.

Use in children
Safety and effectiveness of CILOXAN 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.

Use in renal and hepatic impairment
No studies have been performed using CILOXAN Eye Drops in patients with kidney or liver problems.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Hypersensitivity to quinolones.

4.4 Special warnings and precautions for use

After cap is removed, if tamper evident snap collar is loose, remove before using product.

For ocular use only.

The clinical experience in children less than one year old, particularly in neonates is very limited. The use of CILOXAN 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 CILOXAN eye 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, 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 (see section 4.8).

Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.

CILOXAN 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.

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 CILOXAN 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 CILOXAN Eye Drops, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of CILOXAN Eye Drops. The precipitate does not preclude the continued application of CILOXAN 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 CILOXAN eye drops.

This medicine contains 0.3 mg benzalkonium chloride in each 5 ml which is equivalent to 0.06 mg/ml. Benzalkonium chloride may be absorbed by soft contact lenses and may

change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards.

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

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

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

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.

Pregnancy

There are no adequate data from the use of CILOXAN 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 CILOXAN during pregnancy, unless the therapeutic benefit is expected to outweigh the potential risk to the fetus.

Breastfeeding

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 CILOXAN is administered to nursing women.

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 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 CILOXAN:

System Organ Classification	**MedDRA Preferred 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
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

Description of selected adverse events
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 (see section 4.4). 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 CILOXAN and musculoskeletal and connective tissue adverse reactions.

In isolated cases blurred vision, decreased visual acuity and medication residue have been observed with ophthalmic ciprofloxacin (see section 4.4).

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 CILOXAN 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

.A topical overdose of CILOXAN 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 Antiinfectives
ATC Code: S01A X13.

Mechanism of Action
CILOXAN eye drops, solution contains the fluoroquinolone ciprofloxacin. 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. 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'-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/l, 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≥ 1mg/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 micro-organisms: *Staphylococcus aureus* (methicillin resistant – MRSA) *Staphylococcus epidermidis* (methicillin resistant - MRSE) Staphylococcus lugdunensis Aerobic Gram-negative micro-organisms*:* None Other micro-organisms: None

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

5.2 Pharmacokinetic properties

CILOXAN eye drops, 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. 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%. 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.

There are no pharmacokinetic data available in respect of use in children.

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

Benzalkonium chloride,
disodium edetate,
mannitol, glacial acetic acid,
sodium acetate,
hydrochloric acid/sodium hydroxide,
purified water.

6.2 Incompatibilities

Incompatible with alkaline solutions.

6.3 Shelf life

Unopened 24 months, after opening 28 days.

6.4 Special precautions for storage

Store upright. Do not store above 25°C. Do not refrigerate or freeze

6.5 Nature and contents of container

5 ml Drop-Tainer LDPE bottle and plug with a polystyrene or polypropylene cap.

6.6 Special precautions for disposal

Discard product 28 days after first opening.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited,
2nd Floor, The WestWorks Building, White City Place,
195 Wood Lane,
London,
W12 7FQ
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00101/0994

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10 DATE OF REVISION OF THE TEXT

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