NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CIPROFLOXACIN (Teva), 0.3% w/v, Eye Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains ciprofloxacin hydrochloride 3.5 mg equivalent to ciprofloxacin base 3 mg.

Excipient with known effect: benzalkonium chloride

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Sterile, multiple-dose product, for topical ophthalmic use.

The pH of CIPROFLOXACIN eye drops is approximately 4.5 and the osmolality is approximately 300 mOsM.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of corneal ulcers, conjunctivitis and blepharitis caused by susceptible strains of bacteria in adults and children 12 months of age or older.

4.2 Dose and method of administration

Corneal Ulcers

The recommended dosage regimen for the treatment of corneal ulcers is: Two drops into the affected eye every 15 minutes for the first six hours and then two drops into the affected eye every 30 minutes for the remainder of the first day.

On the second day, instill two drops in the affected eye hourly.

On the third through to the fourteenth day, place two drops in the affected eye every four hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.

Bacterial Conjunctivitis/Blepharitis

The recommended dosage regimen for the treatment of bacterial conjunctivitis is: One drop instilled into the conjunctival sac(s) every two hours while awake for two days and one drop every four hours while awake for the next five days.

4.3 Contraindications

A history of hypersensitivity to ciprofloxacin or any other component of the medication. (see section 6.1).

A history of hypersensitivity to other quinolones, including nalidixic acid, may also contraindicate the use of ciprofloxacin.

4.4 Special warnings and precautions for use

FOR TOPICAL USE ONLY - NOT FOR INJECTION

FOR OCULAR USE ONLY

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 anaphylactic reactions require immediate emergency treatment with adrenaline and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Moderate to severe phototoxicity manifested by an exaggerated sunburn reaction has been observed in some patients who were exposed to direct sunlight while receiving some members of the quinolone class of drugs, including oral ciprofloxacin. Excessive sunlight should be avoided.

General
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. When using CIPROFLOXACIN eye drops one should take into account the risk of a rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Whenever clinical judgment dictates, the patient's eye(s) should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

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 CIPROFLOXACIN 0.3% eye drops should be discontinued at the first sign of tendon inflammation.

CIPROFLOXACIN eye drops contains 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 CIPROFLOXACIN eye drops.

In clinical studies of patients with bacterial corneal ulcer 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 one patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24-72 hours); in five patients, resolution was noted in 10-13 days. In nine 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 three 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 (see 4.8 Undesirable Effects).

Use in Children
Safety and effectiveness in children below the age of 1 year particularly in neonates is very limited and 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.

Use of CIPROFLOXACIN eye drops in neonates with ophthalmia neonatorum of gonococcal or chlamydial 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 medicines and other forms of interaction

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 have been associated with transient elevations in serum creatinine in patients receiving cyclosporin concomitantly.

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

4.6 Fertility, pregnancy and lactation

Pregnancy Category B3

There are no adequate and well controlled studies in pregnant women. As a precautionary measure, it is preferable to avoid the use of CIPROFLOXACIN eye drops during pregnancy. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

See section 5.3 Preclinical safety studies for reproduction studies in animals.

Use in Lactation

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 ciprofloxacin is administered to a nursing mother.

Fertility

Studies have not been performed in humans to evaluate the effect of topical administration of ciprofloxacin on fertility.

4.7 Effects on ability to drive and 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

The most frequently reported drug related adverse reaction was local burning or discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients (see 4.4 Special warnings and precautions for use).

Tabulated adverse reaction data (considered to be related or possible related to treatment), providing comparisons to placebo (to an incidence of 1% or greater in the CIPROFLOXACIN eye drops treatment group), which have been generated from all adult clinical studies with CIPROFLOXACIN eye drops are provided below:

Tabulated Adverse Reaction Data Comparing Incidence (%) Figures

Adverse Reaction	Ciprofloxacin Eye Drops 0.3% (n = 950)	Placebo (n = 202)
Ocular		
Discomfort	9.7	7.9
White precipitate	3.6	-
Foreign body sensation	2.0	-
Hyperaemia/erythema/redness	1.2	1.4
Itching	1.1	1.9
Special Senses		
Taste abnormality	5.0	-

"-" Incidence less than 1%

Uncommon ophthalmic events (occurring in less than 1% and greater than 0.1% of patients) included lid margin crusting, crystals/scales, dryness/dry eye, discharge, corneal staining, keratopathy/keratitis, tearing, photophobia, pain, vision decrease, chemosis, corneal infiltrates, inflammation, blurred vision, corneal toxicity, allergy, intolerance, lid oedema, heavy sensation, swelling, conjunctival reaction, numbing sensation, conjunctivitis, punctate epithelial erosion and progression of infiltrate.

Uncommon systemic events (occurring in less than 1% and greater than 0.1% of patients) included nausea and sinus drainage.

Post-marketing Experience
The following adverse reactions are classified according to the following convention: very common, common, uncommon, rare, very rare, or not known (cannot be estimated from the available data), according to system organ classes. 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.

Infections and infestations
Rare (> 0.01% to ≤ 0.1%): hordeolum, rhinitis

Immune system disorders
Rare (> 0.01% to ≤ 0.1%): hypersensitivity

Nervous system disorders
Common (> 1% to < 10%): dysgeusia

Uncommon (> 0.1% to ≤ 1%) headache

Rare (>0.01% to ≤ 0.1%): dizziness

Eye disorders
Common (> 1% to < 10%): corneal deposits, ocular discomfort, ocular hyperaemia

Uncommon (> 0.1% to ≤ 1%) 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 (> 0.01% to ≤ 0.1%): 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 (> 0.01% to ≤ 0.1%): ear pain

Respiratory, thoracic and mediastinal disorders:
Rare (> 0.01% to ≤ 0.1%): paranasal sinus hypersecretion

Gastrointestinal disorders:
Uncommon (> 0.1% to ≤ 1%) nausea
Rare (> 0.01% to ≤ 0.1%): diarrhoea, abdominal pain

Skin and subcutaneous tissue disorders:
Rare (> 0.01% to ≤ 0.1%): dermatitis

General disorders and administration site conditions:
Rare (> 0.01% to ≤ 0.1%): drug intolerance

Investigations
Rare (> 0.01% to ≤ 0.1%): laboratory test abnormal

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

Musculoskeletal and connective tissue disorders
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 ciprofloxacin dye drops and musculoskeletal and connective tissue adverse reactions.

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 ciprofloxacin eye drops. The precipitate does not preclude the continued use of ciprofloxacin eye drops, nor does it adversely affect the clinical course of the recovery process.

The most common adverse events reported in the post-marketing period for ciprofloxacin eye drops were precipitate in the eye, eye discomfort, non-specific ocular irritation and foreign body sensation. No adverse events were reported at an incidence greater than 1:100, 000.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

A topical overdose of CIPROFLOXACIN eye drops may be flushed from the eye(s) with warm tap water. Accidental oral ingestion of CIPROFLOXACIN is not likely to be associated with toxicity.

Treatment of any exposure is symptomatic and supportive.

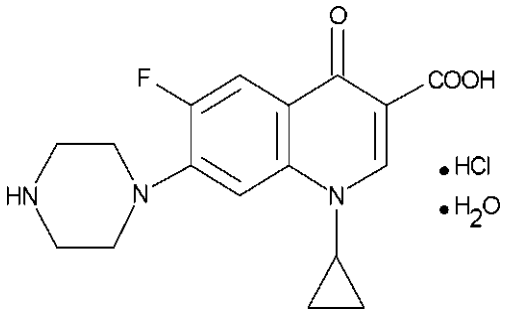
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antiinfectives, Fluoroquinolones, S01AE03

Ciprofloxacin, a faint to light yellow crystalline powder which is soluble in water, is a fluoroquinolone antibacterial. The chemical structure of ciprofloxacin hydrochloride is represented as:



Empirical formula: $C_{17}H_{18}FN_30_3.HCl.H_20$
Molecular weight: 385.8
Chemical name: The monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

CAS Registry Number: 86393-32-0

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms, possessing the greatest antibacterial activity of all quinolones.

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see 4.1 Therapeutic Indications):

Gram-Positive:
Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Viridans group of *Streptococcus*

Gram-Negative:
Pseudomonas aeruginosa
Serratia marcescens
Haemophilus influenza

Other Organisms:
Most strains of *Pseudomonas cepacia* and some strains of *Pseudomonas 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). A plasmid-mediated bacterial resistance does not appear to occur with the fluoroquinolone class of antibiotics, however, parallel resistance is seen with this group of gyrase inhibitors.

Due to its special mode of action there is no cross-over resistance between ciprofloxacin and other antibacterial compounds with different chemical structures, such as ß-lactam antibiotics, aminoglycosides, tetracyclines, macrolide and peptide antibiotics as well as sulfonamides, trimethoprim and nitrofuran derivatives.

Clinical Safety and Efficacy
Following therapy with Ciprofloxacin eye drops 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialization occurred in about 92% of the ulcers. In 3 and 7 day multicentre clinical trials, 52% of the patients with conjunctivitis and positive conjunctival cultures were clinically cured and 70-80% had all causative pathogens eradicated by the end of treatment.

5.2 Pharmacokinetic properties
A systemic absorption study was performed in which Ciprofloxacin eye drops were administered in each eye every two hours while awake for two days followed by every four hours while awake for an additional 5 days. The maximum reported plasma concentration of ciprofloxacin was 4.7 ng/mL (some 450-fold less than levels observed following simple 250 mg oral administration). The mean concentration was usually less than 2.5 ng/mL.

5.3 Preclinical safety data
Reproduction studies have been performed in rats and mice at doses up to six 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.

Toxicological Properties
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.

Acute topical ocular toxicology studies performed in rabbits employing an exaggerated topical ocular exposure to 0.3%, 0.75%, or 1.5% ciprofloxacin ophthalmic solution showed findings that were minimal and transient in nature, confined to the conjunctiva and generally comparable to those effects observed in the untreated control and vehicle control groups.

A subchronic, one-month topical ocular irritation study of 0.3% to 1.5% ciprofloxacin ophthalmic solution did not demonstrate any apparent systemic or ocular toxicity in rabbits.

Mutagenicity
Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- *Salmonella* Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V_{79} Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively) and rats (oral doses up to 241 mg/kg/day and 328 mg/kg/day in males and females, respectively) showed no evidence of carcinogenicity.

Other Animal Studies

Special studies included a cataractogenic potential study of systemic ciprofloxacin in rats. The results indicated that ciprofloxacin was not co-cataractogenic. An intravenous study of ciprofloxacin at dose levels up to 20 mg/kg over a 6-month period in Rhesus monkeys indicated there were no signs of changes in lens transparency due to the administration of ciprofloxacin.

The arthropathogenic potential of some quinolones in immature animals after oral administration is recognised. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride (0.06 mg/mL; preservative), Glacial acetic acid, Sodium acetate anhydrous, Mannitol, Disodium edetate, Sodium Hydroxide, Hydrochloric acid and Water for injection.

6.2 Incompatibilities

Alkaline solutions

6.3 Shelf life

24 months

28 days opened stored below 25°C. Discard container 4 weeks after opening.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Do not refrigerate. Do not freeze.

6.5 Nature and contents of container

5 mL Bottle

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

22 September 2016

10. DATE OF REVISION OF THE TEXT

13 February 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Various	Reformat information under appropriate headings and minor editorial changes.