NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CIPROXIN® HC Ear Drops ciprofloxacin 0.2% and hydrocortisone 1%.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciproxin HC Ear Drops contain 23.3 mg ciprofloxacin hydrochloride (equivalent to ciprofloxacin 0.2 % w/v) and hydrocortisone 100 mg (1% w/v).

Excipient with known effect

Benzyl alcohol 9 mg in 1 mL as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The treatment of acute bacterial external otitis caused by organisms susceptible to the action of ciprofloxacin, including *Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter anitratus (baumannii), Stenotrophomonas maltophilia, Enterobacteriaceae, Enterococcus faecalis* and *Proteus mirabilis.*

4.2. Dose and method of administration

For children (aged two years and older) and adults, three drops of the suspension should be instilled into the affected ear twice daily for seven days. The bottle should be shaken well, immediately before use.

The patient should tilt the head to one side with the affected ear upward and then the drops should be instilled. This position should be maintained for a minimum of 30 seconds to facilitate penetration of the drops into the external ear canal. Repeat, if necessary, for the opposite ear.

Patient instructions for use/handling

Remove the closure and put the dropper assembly in place on the bottle. Ciproxin HC Ear Drops is a ready to use when dropper assembly is placed on the bottle.

Shake well immediately before using.

Warm to room temperature prior to application.

Avoid contaminating the dropper with material from the ear, fingers or other sources.

Discard unused portion after therapy is completed.

Keep all medicines out of the reach of children.

4.3. Contraindications

Ciproxin HC Ear Drops are contraindicated in patients being treated for necrotizing malignant otitis externa. This condition, which is particularly common in diabetes, should be treated with systemic anti-pseudomonal agents.

Ciproxin HC Ear Drops should not be used to treat viral or fungal infections of the external ear canal unless it is suspected that there is a secondary bacterial infection present which will respond to topical ciprofloxacin.

Ciproxin HC Ear Drops is not indicated for the treatment of otitis media.

Known hypersensitivity to benzyl alcohol, hydrocortisone, ciprofloxacin or other quinolone antimicrobial agents, or any of the excipients listed under 6.1) below.

4.4. Special warnings and precautions for use

The safety and efficacy of Ciproxin HC Ear Drops have not been studied in the presence of a perforated tympanic membrane. Ciproxin HC Ear Drops are, therefore, not recommended in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones.

Ciproxin HC Ear Drops should be discontinued at the first appearance of any sign of local or general hypersensitivity.

Ciproxin HC Ear Drops are not for ophthalmic use.

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. If an infection is not improved after one week, cultures and susceptibility tests should be performed to verify the identity of the organism and to determine what alternative therapy should be initiated.

Moderate to severe phototoxicity has been observed in some patients exposed to direct sunlight while receiving some members of the quinolone class of medicines, including ciprofloxacin.

The dropper cap contains natural rubber (latex) which may cause severe allergic reactions.

Visual Disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 Interactions with other medicinal products and other forms of interactions

Ciproxin HC Ear Drops should be administered separately, because the compatibility of other medicines with this formulation is unknown. Specific systemic medicine interactions are not expected to occur with Ciproxin HC Ear Drops, because they are minimally absorbed.

4.6 Fertility, pregnancy and lactation

Pregnancy Category B3

No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when Ciproxin HC Ear Drops are used by a pregnant woman.

Refer to Section 5.3 Pre-clinical safety data pregnancy for pre-clinical reproductive studies.

Breast-feeding

Ciprofloxacin/metabolites are excreted in human milk with systemic use. It is not known whether ciprofloxacin or hydrocortisone/metabolites are excreted in human milk following otic topical administration. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

Caution should be exercised with the use of Ciproxin HC Ear Drops since there is no experience of the medicine's safety in nursing mothers.

Effect on fertility

Preclinical data in fertility is included in section 5.3 Preclinical safety data, fertility**.**

4.7 Effects on ability to drive or use machines

There are no known effects of Ciproxin HC Ear Drops on the ability to drive and use machines.

4.8 Undesirable effects

Clinical Trials

There are no placebo controlled studies of the efficacy and safety of Ciproxin HC Ear Drops. In clinical trials against the active control (polymixin B [10,000 IU], neomycin [3.5mg/mL] and hydrocortisone [10mg/mL]), the following adverse events were recorded in more than 1% of patients.

All adverse events* occuring in more than 1% of patients (%)		
Adverse Events	**Ciproxin HC Ear Drops (n=564)**	**Active Control (n=554)**
Any adverse event	18	15
Body as a whole	9	5

All adverse events* occuring in more than 1% of patients (%)		
Adverse Events	**Ciproxin HC Ear Drops (n=564)**	**Active Control (n=554)**
Headache	5	3
Infection	1	0.4
Fever	6	0.4
Digestive System	2	3
Nausea	1.4	0.9
Nervous system	0.3	1.2
Respiratory System	3	2
Skin and appendages	2	2
Pruritus	1.2	0.5
Special senses	4	4
Otitis externa**	2.1	0.9
Otitis media	1	1.1
* Includes any adverse events, whether considered to be medicine-related or not. ** Indicates otitis externa of the non-treated ear,		

During clinical trials, adverse events considered to be at least possibly related to treatment occurred in 3.9% of patients using Ciproxin HC Eye Drops.

Medicine related events reported with an incidence of between 0.1 and 1% were hypoaesthesia, paraesthesia, pruritus, rash, urticaria, ear pain, ear disorder and a sensation of fullness of the ear. Headache (1.2%) has also been reported.

Post Marketing Experience

The following adverse reactions have been reported during clinical studies with Ciproxin HC Ear Drops and 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) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Ear and labyrinth disorders

Common (≥ 1% to < 10%): ear pruritus.

Uncommon (≥ 0.1% to < 1%): ear pain, ear congestion, ear discomfort, ear canal erythema.

Infections and infestations

Uncommon (≥ 0.1% to < 1%): fungal skin infection.

Nervous system disorders

Uncommon (≥ 0.1% to < 1%): dizziness, headache.

Gastrointestinal disorders:

Uncommon (≥ 0.1% to < 1%): nausea.

Skin and subcutaneous tissue disorders

Uncommon (≥ 0.1% to < 1%): skin exfoliation, urticaria, rash, pruritus.

General disorders and administration site conditions:

Uncommon (≥ 0.1% to < 1%): medication residue.

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

Ear and labyrinth disorders

Not known: hypoacusis, tinnitus.

Very rare cases of product residue in the ear canal with or without symptoms such as ear discomfort, hearing disorders, ear pain have been reported during post-marketing experience.

Eye Disorders

Vision Blurred (see Section 4.4 Special Warnings and Precautions for Use).

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

There have been no reports of overdosage with Ciproxin HC Ear Drops in humans. However, in pre-clinical studies guinea pigs treated with at least twenty times the equivalent human dosage showed no toxic effects.

No significant toxic effects are to be expected in an acute otic overdose, nor in the event of accidental ingestion of Ciproxin HC Ear Drops.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sensory organ; otologicals; corticosteroids and antiinfectives; ATC Code SO2CA03.

Mechanism of action

Ciprofloxacin has *in-vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA. Hydrocortisone is a corticosteroid hormone with known and well characterised anti-inflammatory properties.

Pharmacodynamic effects

No information available.

Clinical efficacy and safety

Two pivotal efficacy studies have been conducted with 1697 patients, of which 1410 were evaluable for efficacy. Following therapy with Ciproxin HC Ear Drops for 7 days, 85% of the patients were clinically cured (resolution vs failure), with a bacterial response rate (eradication + presumed eradication vs persistence) of 93% at the end of therapy (EOT). At follow-up (11-31 days after EOT), 94% of patients remained clinically cured. The predominant causative organisms isolated were *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The bacteriological response by causative organism at the end of therapy is shown in Table 1 below.

Organism	**Eradication + presumed eradiation**		**Persistence + indeterminate**	
	n	**%**	**n**	**%**
P. aeruginosa	230	88.1	31	11.9
S. aureus	38	86.4	6	13.6

5.2 Pharmacokinetic properties

Clinical pharmacokinetic studies have not been performed with the Ciproxin HC Ear Drops since the predicted ciprofloxacin serum concentrations after ototopic administration of a 0.2% suspension (total dose per ear per application approximately 180 (g) would be below the existing assay detection limits (limit of quantification 0.5 (g/L). Even if full absorption of the topical dose were seen, peak ciprofloxacin concentrations of only approximately 3 (g/L would be expected at steady state, based on data for oral administration.

Absorption of hydrocortisone after topical administration is generally low, and varies greatly with the site of administration. It would be impossible by serum assay to distinguish the very small contribution due to the exogenous hydrocortisone (total dose per ear per application 0.9 mg) from that due to endogenous cortisol production. Measurements after ototopical administration are not known to have been performed.

5.3 Preclinical safety data

Carcinogenicity

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 1090 (male mice), 1455 (female mice), 241 (male rats) and 328 mg/kg (female rats) were administered for up to 2 years, there was

no evidence that ciprofloxacin had any carcinogenic effects in these species. No long-term studies of Ciproxin HC Ear Drops have been performed to evaluate carcinogenic potential.

Long term studies have not been performed to evaluate the carcinogenic potential of the effect on fertility of topical hydrocortisone.

Mutagenicity

Ciprofloxacin was mutagenic in the mouse lymphoma assay and showed DNA damage in a DNA repair assay *in vitro* but not in an *in vivo* repair assay. Ciprofloxacin was negative in assays for chromosomal damage and cell transformation. Mutagenicity studies with hydrocortisone were negative.

Pregnancy

Reproduction studies have been performed in rats and mice using oral doses of up to 100mg/kg and IV doses up to 30mg/kg and have revealed no evidence of harm to the foetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Studies in animals with hydrocortisone have shown reproductive toxicity,

Animal reproduction studies have not been conducted with Ciproxin HC Ear Drops.

Fertility

Studies performed in rats at oral doses of ciprofloxacin up to 100mg/kg/day revealed no evidence of impairment of fertility.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol as a preservative

Polysorbate 20

Sodium acetate

Glacial acetic acid

Phospholipon 90 H

Sodium chloride

Polyvinyl alcohol

Purified water.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

24 months unopened (without dropper assembly in place).

14 days when opened and when dropper assembly is in place.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Do not refrigerate the unopened bottle.

Store below 25°C. Protect from light. Do not refrigerate the opened bottle when the dropper assembly is in place.

6.5 Nature and contents of container

10 mL glass bottle with a wrapped dropper assembly consisting of a polyethylene pipette, a polypropylene cap and a rubber bulb.

At the time of dispensing the liner-less polypropylene cap is replaced by the dropper assembly.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

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20 March 1998

10. DATE OF REVISION OF THE TEXT

1 July 2020

SUMMARY TABLE OF CHANGES

8 Sponsor	Update to Sponsor address

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