AUSTRALIAN PRODUCT INFORMATION – CIPROXIN® HC (CIPROFLOXACIN AND HYDROCORTISONE) EAR DROPS

1 NAME OF THE MEDICINE

Ciprofloxacin hydrochloride and Hydrocortisone.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPROXIN HC Ear Drops contains 2.33 mg/mL ciprofloxacin hydrochloride (corresponding to 2.0 mg/mL ciprofloxacin), 10 mg/mL hydrocortisone and 9.0 mg/mL benzyl alcohol as preservative.

CIPROXIN HC Ear Drops contain benzyl alcohol as a preservative. Other excipients are: polysorbate 20, sodium acetate, acetic acid-glacial, sodium chloride, hydrogenated soy phosphatidylcholine, polyvinyl alcohol, water-purified. CIPROXIN HC Ear Drops contain soya bean products.

3 PHARMACEUTICAL FORM

CIPROXIN HC Ear Drops is supplied as a non-sterile, slightly viscous white to off-white opaque suspension in a 10 mL bottle with acetous odour with a separately wrapped non-sterile dropper assembly.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CIPROXIN HC Ear Drops are indicated for the treatment of acute bacterial otitis externa, caused by organisms susceptible to ciprofloxacin (see PHARMACOLOGY), in adults and children aged 2 years and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

For children (age 2 and older) and adults

Three drops of the suspension (equivalent to about 0.09 mL CIPROXIN HC Ear Drops containing 0.18 mg ciprofloxacin and 0.9 mg hydrocortisone) should be instilled into the affected ear twice daily for seven days. The bottle should be shaken well, immediately before use.

The patient should be either sitting or lying down with the affected ear turned upwards and then the drops should be instilled. This position should be maintained for 30-60 seconds to facilitate penetration of the drops into the external ear canal. Repeat if necessary, for the opposite ear.

Use in Elderly

No specific limitation.

Use in Children

For children less than 2 years of age, there is insufficient data available.

Use in Hepatic Impairment

No specific limitation.

Use in Renal Impairment

No specific limitation.

4.3 CONTRAINDICATIONS

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, contraindicated in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane.

CIPROXIN HC Ear Drops are also contraindicated in patients being treated for necrotising "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.

Known hypersensitivity to benzyl alcohol, hydrocortisone, ciprofloxacin or other quinolone antimicrobial agents, or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 drugs, 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.

Carcinogenicity, Mutagenicity, Impairment of Fertility

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.

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.

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

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

Use in the elderly

See Section 4.2 Dose and Method of Administration.

Paediatric use

See Section 4.2 Dose and Method of Administration.

Effects on laboratory tests

Specific laboratory test interaction studies have not been conducted with CIPROXIN HC Ear Drops, however such effects are not expected with the use of CIPROXIN HC Ear Drops.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Specific drug interaction studies have not been conducted with CIPROXIN HC Ear Drops. No additions to the formulation are recommended. CIPROXIN HC Ear Drops should be administered separately, because the compatibility of other drugs with this formulation is unknown. Specific systemic drug interactions are not expected to occur with CIPROXIN HC Ear Drops, because they are minimally absorbed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

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

Use in pregnancy – Pregnancy Category B3

Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/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 20 mg/kg, no maternal toxicity was produced in the rabbit and no embryo-toxicity 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. 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.

Use in lactation.

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 topical otic 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 drug, taking into account the importance of the drug to the mother.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (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 [3.5 mg/mL] and hydrocortisone [10 mg/mL]), the following adverse events were recorded in more than 1% of patients.

All adverse events* occurring 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
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 drug-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 Ear Drops. Drug-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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no human data on overdosage with CIPROXIN HC Ear Drops.

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Clinical trials

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 2.

Organism	**Eradication + presumed eradication**		**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 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 µg) would be below the existing assay detection limits (limit of quantification 0.5 µg/L). Even if full absorption of the topical dose were seen, peak ciprofloxacin concentrations of only approximately 3 µg/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

Genotoxicity

Refer to Section 4.4 Special warnings and precautions for use.

Carcinogenicity

Refer to Section 4.4 Special warnings and precautions for use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Shelf life after opening

14 days

6.5 NATURE AND CONTENTS OF CONTAINER

CIPROXIN HC Ear Drops is supplied as a non-sterile, slightly viscous white to off-white opaque suspension in a 10 mL bottle with a separately wrapped non-sterile dropper assembly.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

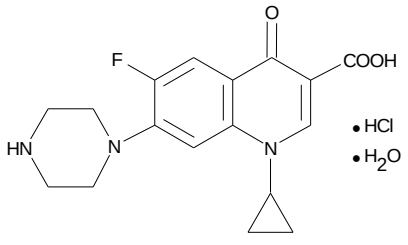
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

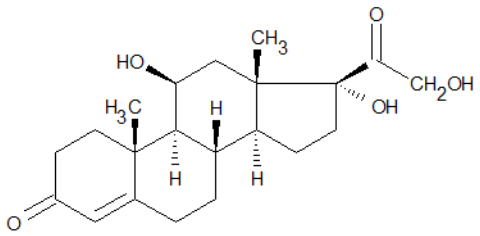
Ciprofloxacin hydrochloride

A synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



Hydrocortisone

A white to off-white crystalline powder, practically insoluble in water, sparingly soluble in acetone and in alcohol, soluble in chloroform with a molecular weight of 362.47. It is an anti inflammatory corticosteroid, with a chemical name of 11ß, 17, 21-trihydroxypregn-4-ene-3,20-dione, and its empirical formula is $C_{21}H_{30}O_5$. Its chemical structure is as follows:



CAS number

Ciprofloxacin hydrochloride (CAS 86393-32-0)

Hydrocortisone (CAS 50-23-7)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

30 November 2007

10 DATE OF REVISION

13 June 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	SmPC format
4.4	Include visual disturbance following corticosteroid use as a precaution.

4.8	Addition of vision blurred as requested by TGA.
2	Addition of declarable substance statement (soya bean products), in accordance with TGO91.

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