

## CIPROXIN HC

### ***Ciprofloxacin 0.2% and Hydrocortisone 1.0% Ear Drops***

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#### **Presentation**

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Each 10 mL bottle (USP type 1 flint glass bottle with a linerless polypropylene closure) contains 23.3 mg ciprofloxacin hydrochloride Ph.Eur. (equivalent to 0.2% ciprofloxacin) and 100 mg hydrocortisone Ph.Eur. In addition 90 mg of benzyl alcohol is included as a preservative.

A single 3-drop dose contains approximately 180(g ciprofloxacin and 0.9mg of hydrocortisone.

A wrapped dropper assembly, consisting of a polyethylene pipette, a polypropylene cap and a rubber bulb are also provided.

At the time of dispensing the linerless polypropylene cap is replaced by the dropper assembly.

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#### **Uses**

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##### ***Actions***

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.

##### ***Pharmacokinetics***

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.

##### ***Clinical Studies***

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.

Organism	Eradication + presumed eradication		Persistence + indeterminate	
	n	%	n	%
<i>P. aeruginosa</i>	230	88.1	31	11.9
<i>S. aureus</i>	38	86.4	6	13.6

### 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*.

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### Dosage and Administration

For children (age two 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.

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### 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 Amalignant 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 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.

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

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### Warnings and Precautions

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 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 installed.

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.

#### 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 100mg/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 Pregnancy

##### Category B3

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.

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 is excreted in human milk with systemic use. It is not known whether ciprofloxacin is 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 medicines safety in nursing mothers.

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## Adverse Effects

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#### 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.

<b>All adverse events* occurring in more than 1% of patients (%)</b>		
<b>Adverse Events</b>	<b>Ciproxin HC Ear Drops (n=564)</b>	<b>Active Control (n=554)</b>
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 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.

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.

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## **Interactions**

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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.

### **Overdosage**

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.

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## **Pharmaceutical Precautions**

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### **Shelf-life**

24 months unopened (without dropper assembly in place).

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

Special precautions for storage

Do not refrigerate. Protect from direct sunlight.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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Ear Drops, 10 mL with dropper.

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## Further Information

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### *List of excipients*

Polysorbate 20 (Ph.Eur.), sodium acetate (Ph.Eur.), glacial acetic acid (Ph.Eur.), benzyl alcohol (Ph.Eur.), phospholipon 90H, sodium chloride (Ph.Eur.), polyvinyl alcohol, purified water (Ph.Eur.).

### *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 product when dropper assembly is placed on the bottle.

Avoid contaminating the dropper with material from the ear, fingers or other sources. Warm to room temperature prior to application. **Shake well immediately before using.**

Protect from direct sunlight.

Do not refrigerate.

Discard unused portion after therapy is completed.

Keep all medicines out of the reach of children.

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## Name and Address

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## Date of Preparation

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