PRODUCT MONOGRAPH

CIPRO® HC OTIC SUSPENSION

(Ciprofloxacin Hydrochloride and Hydrocortisone)

Antibacterial/Corticosteroid

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(ciprofloxacin hydrochloride and hydrocortisone)

THERAPEUTIC CLASSIFICATION

Antibacterial/Corticosteroid

ACTION AND CLINICAL PHARMACOLOGY

CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride, USP and hydrocortisone, USP) contains the synthetic broad spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, hydrocortisone, in a preserved, non-sterile suspension for otic use. 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 has been added to suppress the inflammatory response accompanying bacterial infection.

The pharmacology of CIPRO® HC OTIC SUSPENSION has not been specifically studied. Measurable systemic availability of hydrocortisone and ciprofloxacin after ototopic administration is not expected.

INDICATION AND CLINICAL USE

CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone) is indicated for the treatment of acute diffuse bacterial external otitis caused by susceptible strains of Staphylococcus aureus, Pseudomonas aeruginosa and Proteus mirabilis.

(See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone) is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. CIPRO® HC OTIC SUSPENSION should not be used if the tympanic membrane is perforated. Use of products containing corticosteroids is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.

WARNINGS

Not for ophthalmic use.

Not for injection.

CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone) should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

PRECAUTIONS

General:

As with other antibiotic preparations, use of this product may result in overgrowth of nonsusceptible organisms, including fungi. If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment.

Anaphylactic reactions including cardiovascular collapse have occurred rarely in patients receiving therapy with CIPRO®, CIPRO® I.V. and CIPRO® Oral Suspension (ciprofloxacin hydrochloride tablets, ciprofloxacin injection and ciprofloxacin oral suspension). These reactions may occur within the first 30 minutes following the first dose and may require epinephrine and other emergency measures.

Sensitization and irritation due to dermal applications of topical corticosteroids have been noted in rare instances. Allergic contact dermatitis from corticosteroids is usually diagnosed by observing failure to heal rather than clinical exacerbation.

Pregnancy:

This drug should be used in pregnant women only if in the physician's opinion, the benefit clearly outweighs any potential risks.

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.

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg and IV doses up to 30 mg/kg and 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 embryotoxicity or teratogenicity was observed.

Animal reproduction studies have not been conducted with CIPRO® HC OTIC SUSPENSION. No adequate and well controlled studies of CIPRO® HC OTIC SUSPENSION have been performed in pregnant women.

Nursing Mothers:

Ciprofloxacin is excreted in human milk with systemic use. It is not known whether topically applied CIPRO® HC OTIC SUSPENSION is excreted in human milk. No adequate and well controlled studies in nursing women have been conducted. Because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Pediatric use:

Safety and efficacy of CIPRO® HC OTIC SUSPENSION in children less than two years of age has not been demonstrated. CIPRO® HC OTIC SUSPENSION has been used in 123 children between the ages of two and twelve years and a 0.2% ciprofloxacin otic solution has been used in 114 children between the ages of two and twelve years. No serious adverse event was reported in these patients. Ciprofloxacin and quinolone-related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration.

(See **DOSAGE AND ADMINISTRATION)**

ADVERSE REACTIONS

During clinical investigation with CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone), adverse events that were considered likely to be related to the drug product

occurred in 3.5% of patients treated. Adverse events with at least a remote relationship to treatment include headache (1.2%) and pruritus (0.4%). The following treatment-related adverse events were each reported in single patients: migraine, hypesthesia, paresthesia, fungal dermatitis, cough, rash, urticaria, and alopecia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There are no human data pertaining to the overdosage of CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone). However, guinea pigs treated with at least twenty times the equivalent human dosage showed no ototoxic effects.

DOSAGE AND ADMINISTRATION

SHAKE WELL IMMEDIATELY BEFORE USING.

- For children (age 2 and older) and adults, 3 drops of the suspension should be instilled into the affected ear twice daily for seven days.
- The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 30-60 seconds to facilitate penetration of the drops into the ear.
- Repeat, if necessary, for the opposite ear.
- Discard unused portion after therapy is completed.

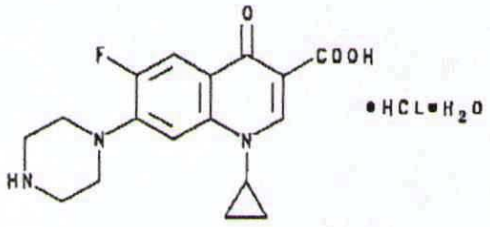
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Ciprofloxacin hydrochloride

Chemical Name: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate.

Structural Formula:

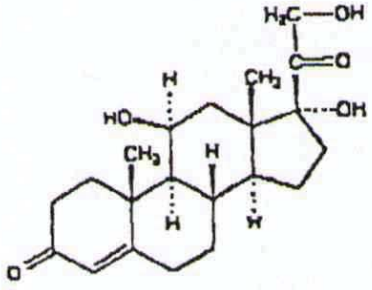


Molecular Formula: $C_{17} H_{18} F N_3 O_3 \cdot HCl \cdot H_2O$

Molecular Weight: 385.8

Proper Name: Hydrocortisone

Chemical Name: pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-, (11β)-, is an anti-inflammatory corticosteroid. Its structural formula is:



Molecular Formula: $C_{21} H_{30} O_5$

Molecular Weight: 362.47

COMPOSITION

Ciprofloxacin hydrochloride equivalent to 2 mg/ml

Hydrocortisone 10 mg/mL

Benzyl alcohol 9 mg/mL

Polyvinyl alcohol

Sodium chloride

Sodium acetate

Glacial acetic acid

Phospholipon 90H (modified lecithin)

Polysorbate

Purified water

Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

STABILITY AND STORAGE RECOMMENDATIONS

Store at 15°C to 25°C. Do not refrigerate. Protect from direct light.

AVAILABILITY OF DOSAGE FORMS

CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone) is supplied as a white to off-white opaque suspension in a 10 ml multidose bottle with a dropper dispenser.

INFORMATION FOR THE CONSUMER

Please read this information carefully. If you have any questions or concerns about CIPRO® HC OTIC SUSPENSION ask your doctor or pharmacist.

What is CIPRO® HC OTIC SUSPENSION?

CIPRO® HC OTIC SUSPENSION is the brand name for ciprofloxacin hydrochloride and hydrocortisone. It is only available by prescription from your doctor.

Your doctor has prescribed CIPRO® HC OTIC SUSPENSION for your swimmer's ear or "otitis externa", a fairly common infection of the outer ear (the area outside the eardrum) and the ear canal. This infection may cause some of the following: inflammation, pain, irritation, itching, temporary hearing loss or "buzzing" in the ear, and a yellowish-green pus discharge from the ear.

How Does CIPRO® HC OTIC SUSPENSION Work?

CIPRO® HC OTIC SUSPENSION is a medication that stops bacteria from growing (an antibacterial) combined with a substance called hydrocortisone, which prevents inflammation (an anti-inflammatory). The antibacterial part of CIPRO® HC OTIC SUSPENSION works by destroying the bacteria that caused the ear infection, while the hydrocortisone helps stop the resulting inflammation and pain.

Important Points to Note Before You Start Taking CIPRO® HC OTIC SUSPENSION.

Although CIPRO® HC OTIC SUSPENSION is effective, there are some people who should not take it. Talk to your doctor if you:

- are allergic to antibiotics or corticosteroids.
- are pregnant, planning to become pregnant or think you may be pregnant. If you become pregnant while taking CIPRO® HC OTIC SUSPENSION, stop taking it and tell your doctor right away.
- are breast-feeding.
- have a perforated eardrum (i.e. a hole in the ear drum).
- have any viral or fungal infection of the outer ear or ear canal, including chicken pox and herpes simplex.
- have already taken CIPRO® HC OTIC SUSPENSION, hydrocortisone or any antibiotic similar to ciprofloxacin (i.e. the quinolone class of antimicrobials) and developed a reaction.

Do not use CIPRO® HC OTIC SUSPENSION in children under 2 years of age.

How to Take CIPRO® HC OTIC SUSPENSION.

Always follow your doctor's instructions carefully and keep taking your medication for the prescribed amount of time, even if you feel better. These guidelines will help you use your medication properly:

- Shake the bottle well just before using.
- Lie with the affected ear upward and then place drops in the ear.
- Using the dropper, put 3 drops in the ear twice a day for 7 days.
- Hold this position for 30-60 seconds to allow the drops to completely go into your ear. Repeat, if necessary, for the opposite ear.

- Only use the dropper supplied with the medication. Avoid touching the dropper to the ear, fingers or any other areas from which it could become contaminated. Not for injection. Not for use in the eye.
- Throw away any unused portion after your treatment is completed.
- Talk to your doctor if you experience any side effects (see below).

After Taking CIPRO® HC OTIC SUSPENSION.

Sometimes a medicine can cause an effect besides the one it is supposed to have. Although some people do not have any side effects when taking CIPRO® HC OTIC SUSPENSION, all medicine can cause some kind of side effects in certain people.

Some side effects may come and go, but you should mention them to your doctor as soon as possible if they become persistent or begin to bother you. These include:

- skin rash, irritation or particular sensitivity such as:
  - itching
  - hives
  - decreased sensitivity to touch
  - numbness, prickling sensation, tingling, increased sensitivity
- hair loss
- headache/migraine
- coughing
- dizziness
- overgrowth of fungi, signs of which may include increased itchiness in ear canal, the presence of debris in ear canal, and/or increased discharge from the ear.

Some people may have other types of reactions, so if you notice any other effects, tell your doctor or pharmacist.

If your ear infection is not better after using the medicine for one week (or as long as your doctor recommended) follow-up with your doctor.

Storing Your Medicine.

Store at room temperature (between 15°C to 25°C). Do not refrigerate. Protect from heat and direct light.

What is in CIPRO® HC OTIC SUSPENSON?

CIPRO® HC OTIC SUSPENSION is a white to off-white solution that comes in a 10 mL multi-dose bottle with a dropper. Its main ingredients are: ciprofloxacin hydrochloride (equivalent to 2 mg/mL), hydrocortisone (10 mg/mL), and benzyl alcohol (9 mg/mL).

Other ingredients are: polyvinyl alcohol, sodium chloride, sodium acetate, glacial acetic acid, phospholipon 90H (modified lecithin), polysorbate, purified water, (sodium hydroxide or hydrochloric acid may also be added to balance pH).

What To Do If You Miss a Dose.

If you miss a dose of CIPRO® HC OTIC SUSPENSION, take it as soon as you remember and then go back to taking it as you would normally. If it is time for your next dose, skip the missed dose and take your next dose.

What To Do If An Overdose Is Taken.

If you accidentally put too much CIPRO® HC OTIC SUSPENSION in your ear, you should not expect a problem because the medication stays in your ear and is not absorbed into your body. Call your physician or pharmacist if you notice any unwanted effects.

Further Information

- This medicine is prescribed for you. Do not give it to other people.
- Keep all medicines out of the reach of children.
- Store CIPRO® HC OTIC SUSPENSION at room temperature (15°C to 25°C), away from heat and direct light.

If you need more information about CIPRO® HC OTIC SUSPENSION, talk to your doctor or pharmacist.

MICROBIOLOGY

CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone) has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections of acute otitis externa as described in the INDICATIONS AND CLINICAL USE section:

Staphylococcus aureus
Proteus mirabilis
Pseudomonas aeruginosa

Table 1: Microbiological Data on European and North American Isolates from Patients with Otitis Externa

Strain (Number of Isolates)	Range	MIC_{50}(mg/L)	MIC_{90}(mg/L)
Pseudomonas aeruginosa (483)	≤0.5 - ≥4.0	≤0.5	≤0.5
Staphylococcus aureus (74)	≤0.5	≤0.5	≤0.5
Proteus mirabilis (18)	≤0.5	≤0.5	≤0.5

PHARMACOLOGY

The pharmacology of CIPRO® HC OTIC SUSPENSION (ciprofloxacin hydrochloride and hydrocortisone) has not been specifically studied. Measurable systemic availability of hydrocortisone and ciprofloxacin after ototopic administration is not expected (1,2). The lack of systemic availability of the active components of CIPRO® HC OTIC SUSPENSION has no expected impact on the actions of this topical fomulation. Preclinical studies have shown that CIPRO® HC OTIC SUSPENSION was absorbed through the round window membrane to the perilymph of the cochlea when a 0.2% solution was instilled directly into the middle ear of guinea pigs, or when a Gelfoam soaked in a 0.01% solution of ciprofloxacin was applied to the round window membrane of chinchillas. (3)

TOXICOLOGY

Extensive toxicity studies have been conducted with the oral, intravenous and ophthalmic formulations of ciprofloxacin. These comprehensive studies established the toxicologic and safety profile of ciprofloxacin in a variety of species via these routes of administration. There was no indication of ototoxicity in any of these preclinical studies, however ototoxicity was not a specific endpoint.

A further series of preclinical studies have shown that CIPRO® HC OTIC SUSPENSION and ciprofloxacin in solution are not toxic to the structural components of the inner ear in the guinea pig over a period of up to 30 days and at dose volume expected to be an exaggeration of the human dose. There was, however, evidence of mild decreases in hearing, considered likely to be of middle ear origin, in association with fibrous tissue around an implanted cannula in the middle ear of these animals. In the rabbit, ciprofloxacin was shown to cause mild inflammation of the tympanic membrane, and CIPRO HC OTIC SUSPENSION was shown to be non-irritating to the skin.

In guinea pigs, ciprofloxacin and CIPRO® HC OTIC SUSPENSION were applied directly to the niche of the round window membrane via a cannula in the middle ear. Functional ototoxicity was

assessed by auditory brainstem response (ABR) with increased hearing thresholds as an endpoint. Structural ototoxicity was assessed by microscopic examination of the cochlea with hair cell loss as an endpoint. The volume delivered was estimated to be approximately 20-50 times the volume anticipated to be present at the round window in the case of tympanic membrane perforation in humans. In the 30-day subacute toxicity studies, some of the animals exhibited minor hearing loss when assessed by ABR. However, in none of the animals treated with ciprofloxacin or CIPRO-HC OTIC SUSPENSION was there an increased loss of cochlear hair cells. In these cases the minor hearing loss was considered to be of middle ear origin, associated with fibrous tissue around the cannula implanted in the middle ear. The buildup of fibrous tissue around the cannula, while not confined to the treatment groups, was more prevalent in the treatment groups, suggesting that the test formulations in general may play a role, perhaps in causing mild irritation. There was no significant functional or structural ototoxicity in the subacute studies of duration 7 days or less (4-6).

In rabbits, when ciprofloxacin solution was instilled as a single dose in the middle ear cavities a reversible inflammatory response was seen in the tympanic membrane (7).

A dermal irritancy study was conducted in which rabbits were treated twice daily for 14 days with CIPRO® HC OTIC SUSPENSION. The animals exhibited slight erythema at the site of application. Due to the mild dermal response and the relatively small volume of formulation expected to be present in the middle ear, it is unlikely that the formulation alone (without the cannula) would cause significant irritation in the middle ear and possible ototoxicity in the clinical situation.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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, 2 of the 8 *in vitro* tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of CIPRO® HC OTIC SUSPENSION have been performed to evaluate carcinogenic potential.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 1000 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with CIPRO® HC OTIC SUSPENSION twice per day.

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

Teratogenic Effects:

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 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 CIPRO® HC OTIC SUSPENSION.

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