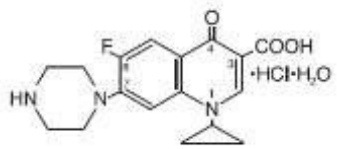
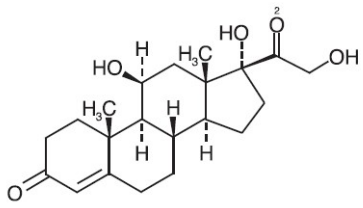
1. NAME OF THE MEDICINAL PRODUCT

CIPROBAY® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension)

CIPROBAY® HC OTIC (ciprofloxacin hydrochloride and hydrocortisone otic suspension) 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, a fluoroquinolone, is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3 \bullet HCl \bullet H_2O$ and its chemical structure is as follows:



Hydrocortisone, pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-(11β)-, is an anti-inflammatory corticosteroid. Its empirical formula is $C_{21}H_{30}O_5$ and its chemical structure is:



2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: Ciprofloxacin hydrochloride (2.329mg/ml), hydrocortisone (micronized) (10mg/ml)
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Ear drops, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPROBAY HC OTIC is indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of Pseudomonas aeruginosa, Staphylococcus aureus, and Proteus mirabilis.

4.2 Posology and method of administration

SHAKE WELL IMMEDIATELY BEFORE USING.

For children (age 1 year and older) and adults, 3 drops of the suspension should be instilled into the affected ear twice daily for seven days. The suspension should be warmed by holding the bottle in the hand for 1-2 minutes to avoid the dizziness which may result from the instillation of a cold solution into the ear canal. 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.

Pediatric use: The safety and efficacy of CIPROBAY HC OTIC have been established in pediatric patients 2 years and older (131 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 2 years, there are no known safety concerns or differences in the disease process in this population which would preclude use of this product in patients one year and older.

4.3 Contraindications

- Hypersensitivity to the active substance(s), to other quinolones or to any of the excipients.
- Viral or fungal infections of the external ear canal including varicella and herpes simplex infections.
- Known or suspected perforation of the eardrum

4.4 Special warnings and precautions for use

NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

- CIPROBAY HC OTIC should be discontinued at the first appearance of any sign of local or general hypersensitivity.

- Prolonged use of antibiotics may result in overgrowth of nonsusceptible organisms. If superinfection occurs, appropriate therapy should be initiated, including fungi. If the infection is not improved after one week of therapy, cultures should be obtained to guide further treatment.

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

- 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. Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been conducted with Ciprobay HC Otic suspension.

4.6 Fertility, pregnancy and lactation

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 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)

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral dose and revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. Studies have not been performed to evaluate the effect on fertility of topical hydrocortisone.

Pregnancy

Teratogenic Effects.

Pregnancy Category C:

There are no or limited amount of data from the use of CIPROBAY HC OTIC in pregnant women. Animal studies with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity. Studies in animals with hydrocortisone have shown reproductive toxicity.
Caution should be exercised when ClPROBAY HC OTIC is used by a pregnant woman.

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 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.

4.7 Effects on ability to drive and use machines

There are no known effects of CIPROBAY HC OTIC on the ability to drive and use machines.

4.8. Undesirable effects

The following adverse reactions have been reported during clinical studies with CIPROBAY HC OTIC 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.

System Organ Classification	**MedDRA Preferred Term (v.14.0)**
Infections and infestations	*Uncommon:* fungal skin infection
Nervous system disorders	*Uncommon:* dizziness, headache, migrane, hypesthesia, paresthesia
Ear and labyrinth disorders	*Common:* ear pruritus *Uncommon:* ear pain, ear congestion, ear discomfort, ear canal erythema
Gastrointestinal disorders	*Uncommon*: nausea
Skin and subcutaneous tissue disorders	*Uncommon:* skin exfoliation, urticaria, rash, pruritus
General disorders and administration site conditions	*Uncommon:* medication residue, cough, alopecia

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

System Organ Classification	**MedDRA Preferred Term (v.16.0)**
Ear and labyrinth disorders	*Not known:* hypoacusis, tinnitus
Eye disorders	Vision blurred

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hydrocortisone has been added to aid in the resolution of the inflammatory response accompanying bacterial Infection.

Microbiology

Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme, DNA gyrase, which is needed for the synthesis of bacterial DNA. Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as betalactams or aminoglycosides.

Ciprofloxacin 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 section 4.1.

Aerobic gram-positive microorganism

Staphylococcus aureus

Aerobic gram-negative microorganism

Proteus mirabilis

Pseudomonas aeruginosa

5.2 Pharmacokinetic properties

The plasma concentrations of ciprofloxacin were not measured following three drops of otic suspension administration because the systemic exposure to ciprofloxacin is expected to be below the limit of quantitation of the assay (0.05 µg/ml)

Similarly, the predicted Cmax of hydrocortisone is within the range of endogenous hydro-cortisone concentration (0-150 ng/ml), and therefore cannot be differentiated from the endogenous cortisol.

5.3 Preclinical safety data

Preclinical studies have shown that CIPROBAY® HC OTIC was not toxic to the guinea pig cochlea when administered intratympanically twice daily for 30 days and was only weakly irritating to rabbit skin upon repeated exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients polysorbate 20, sodium acetate (trihydrate), acetic acid (glacial), benzyl alcohol, lecithin, sodium chloride, polyvinyl alcohol, purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Store between 59-77°F (15°- 25°C). AVOID REFRIGERATION AND FREEZING. Protect from light.
Shake well immediately before using.
Discard unused portion after therapy is completed.

6.4 Nature and content of container

10 mL bottle with a dropper dispenser.

6.5 Special precautions for disposal

No special requirement

6.6 Manufacturer

Refer to folding box.

Rx Only

(Information Issued: Jan 2014.SINv2)

Novartis Pharma AG, Basel, Switzerland