PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Cetraxal 2 mg/ml ear drops solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 2 mg of ciprofloxacin as hydrochloride

Each single-dose ampoule delivers 0.25 ml of solution that contains 0.58 mg of ciprofloxacin hydrochloride monohydrate corresponding to 0.50 mg of ciprofloxacin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops solution.

Clear, sterile, preservative-free aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetraxal 2 mg/ml ear drops solution is indicated for the treatment of acute otitis externa caused by ciprofloxacin susceptible microorganisms (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults and children aged one year and older:
Instil the contents of one single ampoule into the affected ear twice daily for seven days.

Paediatric patients less than one year
The safety and efficacy of Cetraxal in children aged below 1 year of age have not been established. No data are available. See section 4.4.

Instructions for correct use of the product:

- The solution should be warmed, by holding the ampoule in the hand for several minutes, to avoid the dizziness that 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, pulling several times on the auricle. This position should be maintained for around 5 minutes to facilitate penetration of the drops into the ear. Repeat, if necessary, for the opposite ear.
- The patient should be advised to discard the single-dose container after the use, and not keep it for subsequent use.
- In case an otowick/tampon is used to facilitate administration, the first dose should be doubled (2 ampoules instead of 1).

Renal/ hepatic impairment
Since the drug plasma concentration is anticipated to be undetectable, no dosage adjustment for these patient groups is deemed necessary.

4.3 Contraindications

Hypersensitivity to the active substance ciprofloxacin or any member of the quinolone class of antimicrobial agents or to any of the excipients.

4.4 Special warnings and precautions for use

This medicinal product is for auricular use, not for ophthalmic use, inhalation or injection.

Although the disease process in patients less than one year old is similar to that in older children, the safety and efficacy of this product have not been established in paediatric patients less than one year old.

Cetraxal 2 mg/ml should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. 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.

As with other antibiotic preparation, the use of this product may result in overgrowth of non-susceptible organisms, including bacterial strains, yeast and fungi. If superinfection occurs, appropriate therapy should be initiated.

If after one week of therapy some signs and symptoms persist, further evaluation is recommended to reassess the disease and the treatment.
Some patients taking systemic quinolones have shown moderate to severe skin sensitivity to sun. Due to the site of administration, it is unlikely that this product may show photoallergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with Cetraxal 2 mg/ml ear drops solution.

Due to low plasma level anticipated after application in the ear, it is unlikely that ciprofloxacin may show systemic interaction with other drugs.

It is recommended not to use other ear preparations concomitantly.

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of ciprofloxacin otic solution 0.2% in pregnant women. There are moderate amount of data from the use oral ciprofloxacin in pregnant women. No reproductive toxicity has been performed after otic administration. However after systemic exposure, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Since systemic exposure to ciprofloxacin is negligible after otic administration, thus no effects are anticipated during pregnancy. Cetraxal can be used during pregnancy.

Lactation
Ciprofloxacin is excreted in human milk after systemic use. It is not known whether ciprofloxacin is excreted in human milk after otic use. No effects on the breast-fed newborn are anticipated since the systemic exposure of the breast-feeding woman to ciprofloxacin is negligible. Cetraxal can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Cetraxal 2 mg/ml ear drops solution has no influence on the ability to drive and use machines.

4.8 Undesirable effects

In a Phase III clinical trial, a total of 319 patients were treated with Cetraxal 2 mg/ml ear drops solution.

The most commonly reported adverse reactions are: ear pruritus occurring in 0.9% of patients treated with ciprofloxacin, and headache and application site pain, both occurring in approximately 0.6 % of patients.

All treatment related adverse reactions are uncommon (≥1/1000 to <1/100) and are listed below.

Ear and Labyrinth Disorders
Uncommon: Ear pruritus, tinnitus

Nervous System Disorders
Uncommon: Dizziness, headache

Skin and subcutaneous disorders
Uncommon: Dermatitis

General Disorders and Administration Site Conditions
Uncommon: Application Site Pain

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome, and urticaria occur very rarely.

4.9 Overdose

The potential risk of overdose with this single-dose preparation is negligible since the total amount of ciprofloxacin per pack is 7.5 mg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: S02AA15 Sensory organs. Otologicals. Antiinfectives.

Mechanism of action
As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship
No pharmacodynamic relationship has been described for topical administration. With local pharmaceuticals forms, the concentration attained *in situ* are far higher than plasma concentrations.

Mechanism of resistance.
In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of crossresistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity
Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	*Susceptible*	*Resistant*
Pseudomonas	*S ≤ 0.5 mg/L*	*R > 1 mg/L*
Staphylococcus spp.	*S ≤ 1 mg/L*	*R > 1 mg/L*

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Based on present data the following table represents susceptibility of ciprofloxacin tothe leading pathogens in the approved indication.

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram positive micro-organisms *Staphylococcus aureus*
Aerobic Gram negative micro-organisms *Pseudomonas aeruginosa*

NB: With local pharmaceuticals forms, the concentrations attained in situ are far higher than plasma concentrations. Some doubts remain as to the kinetics of concentrations *in situ*, the local physical and chemical conditions which may modify the activity of the antibiotic and the stability of the product *in situ*.

5.2 Pharmacokinetic properties

The plasma concentrations of ciprofloxacin were not measured following Administration of 0.25 ml Cetraxal 0.2% (total dose: 0.5 mg ciprofloxacin). It is expected that systemic plasma levels will be no detectable or very low, although no significant systemic passage of ciprofloxacin is expected under normal condition of use. Even if the entire amount of ciprofloxacin was absorbed following bilateral ear administration (1mg total dose) it is doubtful that a detectable plasma concentration of this drug would result in a human considering 180L as volume of distribution of ciprofloxacin (EUCAST information) and 5ng/ml as the detection limit.

5.3 Preclinical safety data

No significant findings were seen in carcinogenicity or reproductive and developmental toxicity studies. Ciprofloxacin is well tolerated when applied to the external ear canal. Skin tolerance studies using both intact and abraded skin revealed no findings on intact skin and only a mild erythema in one of three animals from the abraded skin group.

In test animals, toxicity was only observed at doses which are high above compared to the highest dose used in the ear.

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested following oral administration. The degree of cartilage involvement was found to be dependent on age, species and dosage. With 30 mg/kg ciprofloxacin the effect on the joint was minimal.

While the joints of some species of juvenile animals are sensitive to the degenerative effects of fluoroquinolones (primarily the dog), young adult guinea pigs dosed in the middle ear with ciprofloxacin for one month exhibited no drug related structural or functional changes of the cochlear hair cells and no lesions in the ossicles.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (E1201)
Glycerine (E422)
Purified water
Sodium hydroxide (E524) and lactic acid (E270) (for pH-adjustment).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

The ampoule contents should be used immediately after opening the single dose ampoule. Any unused contents should be discarded.

Shelf-life after first opening of the pouch: 8 days

6.4 Special precautions for storage

Store below 30ºC. Store in the original packaging in order to protect from light.

6.5 Nature and contents of container

The solution 0.2% is contained within a formed low-density polyethylene (LDPE) ampoule. Each single ampoule delivers 0.25 ml dropwise. The ampoules are contained in an aluminium foil overwrap pouch for protection.

Each pack contains 15 ampoules.

6.6 Special precautions for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

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