SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cetraxal 2 mg/ml ear drops solution in single-dose container.

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 in single-dose container.
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 in adults and children older than 1 year with an intact tympanic membrane, 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.

Method of administration
- Precautions to be taken before handling or administering the medicinal 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 listed in section 6.1.

4.4 Special warnings and precautions for use

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

In otic use meticulous medical monitoring is required in order to be able to determine in a timely manner the possible necessity of other therapeutic measures.

Paediatric population

The safety and efficacy of this product have been established in paediatric patients 1 year and older in controlled clinical trials. Although very limited data are available in patients less than age 1 year treated for acute otitis externa, there are no differences in the disease process itself, in this patient population, which would preclude use of this product in patients less than one year of age. Based upon the very limited data, the prescribing physician should weigh the clinical benefits of use against the known and possibly unknown risks when prescribing in patients less than age 1 year.

The safety and efficacy of Cetraxal have not been studied in the presence of a perforated tympanic membrane. Therefore, Cetraxal should be used with caution in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane.

Cetraxal 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

No interaction studies have been performed with Cetraxal.

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 Fertility, 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.

Fertility
Studies in animals with oral administration of ciprofloxacin do not indicate any effects on fertility.

4.7 Effects on ability to drive and use machines

Cetraxal has no or negligible 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. 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.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V*.

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 pharmaceutical 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 cross-resistance 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.

Breakpoints

For most topical agents there are limited pharmacological data and no data relating treatment to outcome. For this reason EUCAST proposes that epidemiological cut-off values (ECOFFs) are used to indicate susceptibility to topical agents.
Epidemiological cut-off values according to EUCAST. ECOFF ≤ mg/ml

- *Enterobacteriaceae* 0.125 mg/l
- *Staphylococcus* spp. 1 mg/l
- *Pseudomonas aeruginosa* 0.5 mg/l

Prevalence of resistance may vary according to geographical zone and weather for the selected microorganisms. Local information on resistance should be available, particularly in the case of serious infections. This information only provides an approximate orientation as to the probability of the microorganism being sensitive to this antibiotic.

Based on present data the following table represents susceptibility of ciprofloxacin to the 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 pharmaceutical 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 both intact and abraded skin in the external ear canal.
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-K-90-F (E1201)
Glycerol (E422)
Purified water
Sodium hydroxide (E524) and lactic acid (E270) (for pH-adjustment).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

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 MARKETING AUTHORISATION HOLDER

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