SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetraxal Plus 3 mg/ml + 0.25 mg/ml ear drops solution in single-dose container

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains ciprofloxacin hydrochloride equivalent to 3 mg ciprofloxacin and 0.25 mg of fluocinolone acetonide.
Each single-dose container (0.25 ml) delivers 0.75 mg of ciprofloxacin and 0.0625 mg of fluocinolone acetonide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops, solution in single-dose container (ear drops).
Colourless or slightly yellow, clear aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetraxal Plus is indicated in adults and in children aged 6 months and older for the following infections:

- Acute otitis externa (AOE)
- Acute otitis media in patients with tympanostomy tubes (AOMT)

caused by ciprofloxacin susceptible microorganisms (see sections 4.2, 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

Posology

Adults and elderly population

Acute otitis externa and acute otitis media with tympanostomy tubes: Instil the contents of one single-dose container into the affected ear canal every 12 hours for 7 days.

No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Renal/ hepatic impairment

No dosage adjustment is deemed necessary.

Paediatric population

The dosage in children aged 6 months and older is the same as for adults for both indications.

Method of administration

Auricular use.

Precautions to be taken before handling or administering the medicinal product

The solution should be warmed before its use, by holding the bottle in the hand for several minutes. This will avoid the discomfort 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 for patients with otitis externa the drops should be instilled pulling several times on the auricle. For patients with acute otitis media with tympanostomy tubes, the tragus should be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for around 1 minute to facilitate penetration of the drops into the ear.

Repeat, if necessary, for the opposite ear.

4.3 Contraindications

Hypersensitivity to the active substances ciprofloxacin or fluocinolone acetonide or any member of the quinolone class of antimicrobial agents or to any of the excipients listed in section 6.1.

Viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections.

4.4 Special warnings and special precautions for use

This medicinal product is for auricular use only, not for ophthalmic use, inhalation or injection. This medicine should not be swallowed or injected.

If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumour. If after the treatment some signs and symptoms persist, further evaluation is recommended to reassess the disease and the treatment.

Cetraxal Plus 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 preparations, 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.

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 produce photoallergic reactions.

Corticosteroids may reduce resistance to, and aid in, the establishment of bacterial, viral, or fungal infections and mask the clinical signs of an infection, preventing recognition of ineffectiveness of the antibiotic, or may suppress hypersensitivity reactions to substances in the product.
Visual disturbance

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.

Paediatric population
Safety and efficacy of Cetraxal Plus have not been established in children younger than 6 months. Under exceptional circumstances, Cetraxal Plus treatment could be used in this sub-paediatric population after a very careful benefit/risk evaluation by the prescribing physician taking into account that although there are no known safety concerns or differences in disease process to preclude use in these children, clinical experience is insufficient in these specific subgroups of paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Cetraxal Plus. However, due to negligible plasma levels observed after application in the ear (see section 5.2), it is unlikely that ciprofloxacin or fluocinolone acetonide may show clinically meaningful systemic interaction with other drugs.

The systemic administration of some quinolones has been shown to enhance the effects of the oral anticoagulant, warfarin, and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Oral administration of ciprofloxacin has been shown to inhibit cytochrome P450 CYP1A2 and CYP3A4 isozymes, and alter the metabolism of methylxanthine compounds (caffeine, theophylline). Following topical otic administration of Cetraxal Plus, ciprofloxacin plasma concentrations are low, and it is unlikely that an interaction involving P450 metabolism with concomitant medications would result in clinically relevant changes in plasma levels of methylxanthine compounds.

It is recommended not to use other ear preparations concomitantly. If more than one medicine needs to be administered by this route, it is advised to administer them apart.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data available on administration of ciprofloxacin to pregnant women indicates no malformative or foeto/neonatal toxicity. Since systemic exposure to ciprofloxacin will be very low no effects are anticipated on the foetus. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from fluocinolone acetonide.

Before administering the medicine, an assessment should be made on the benefits of the treatment outweighing the possible risk.

Breastfeeding
Ciprofloxacin is excreted in breast milk. Since systemic exposure to ciprofloxacin will be very low no effects are anticipated on the children that are breastfeeding.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

Caution should be exercised when Cetraxal Plus is administered to a nursing woman.

Fertility
No animal studies have been performed to evaluate the effect on fertility of Cetraxal Plus.

4.7 Effects on the ability to drive and use machines

Cetraxal Plus has no influence on the ability to drive and use machines due to the route of administration and the conditions of use.

4.8 Undesirable effects

Tabulated summary of adverse events
The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term**
Infections and infestations	*Uncommon:* candidiasis, ear infection fungal, contralateral otitis media
Nervous system disorders	*Common:* dysgeusia *Uncommon:* paraesthesia (tingling in ears), dizziness, headache, crying
Ear and labyrinth disorders	*Common:* ear pain, ear discomfort, ear pruritus *Uncommon:* hypoacusis, tinnitus, otorrhoea, ear congestion, tympanic membrane disorder, auricular swelling
Eye disorders	*Not known:* Vision, blurred (see also section 4.4)
Vascular disorders	*Uncommon:* flushing
Gastrointestinal disorders	*Uncommon:* vomiting
Skin and subcutaneous tissue disorders	*Uncommon:* skin exfoliation, rash erythematous, rash, granulation tissue
General disorders and administration site conditions	*Uncommon:* irritability, fatigue
Investigations	*Uncommon:* medication residue
Injury, poisoning and procedural complications	*Uncommon:* device occlusion (tympanostomy tube obstruction)

Description of selected adverse reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were

accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching.
Ruptures of the shoulder, hand, Achiles or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic fluoroquinolones indicate that the risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including the Achiles tendon. To date, clinical and post marketing data have not demonstrated a clear association between otic administration of ciprofloxacin and these musculoskeletal and connective tissue adverse reactions.

Paediatric population
Cetraxal Plus has been shown to be safe in paediatric patients 6 months of age or older.

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 [TO BE COMPLETED NATIONALLY].

4.9 Overdose

No case of overdose has been reported.

Due to negligible plasma levels observed after application in the ear, it is unlikely that topically applied ciprofloxacin or fluocinolone acetonide may show clinically meaningful systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse, the features of hypercortisolism may appear.

The limited holding capacity of the ear canal for topical otic products practically precludes overdosing via the ototopical route. However, oral ingestion of Cetraxal Plus resulting in overdose or long-term ototopical therapy may produce suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Although decreases in paediatric growth velocity and/or suppression of cortisol plasma concentrations may be more pronounced after substantial overdose or prolonged treatment (e.g. several months) with Cetraxal Plus, the effect is expected to be transient (days to weeks) and easily reversible with no long-term sequelae.

If the preparation is accidentally swallowed, treatment will include gastric emptying by induced vomiting or gastric lavage, the administration of activated charcoal and antacids containing magnesium or calcium.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Otological preparations: corticosteroids and antiinfectives in combination, ATC Code: S02CA05.

Fluocinolone acetonide

Fluocinolone acetonide is a synthetic fluorinated corticosteroid with anti-inflammatory, antipruritic, and vasoconstrictive properties. Early anti-inflammatory effects of topical

corticosteroids include the inhibition of macrophage and leukocyte movement and activity in the inflamed area by reversing vascular dilation and permeability. Later inflammatory processes such as capillary production, collagen deposition, keloid (scar) formation also are inhibited by corticosteroids.

Ciprofloxacin

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.

Mechanism of resistance
The mutation in genes encoding ciprofloxacin targets (gyr A, gyrN, parC, parE) represent the main mechanism of ciprofloxacin resistance in *P. aeruginosa*. Another mechanism of resistance described is overexpression of the efflux pumps, in particular Mex (Multiple EffluX) gene. The single mutations do not necessarily result in clinical resistance, but multiple mutations generally result in clinical resistance.

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.

EUCAST Clinical Breakpoint for ciprofloxacin (Table v. 7.1, valid from 2017-03-10):

Microorganisms	Sensible (S)	Resistant (R)
Staphylococcus species	S ≤ 1 mg/l	R > 1 mg/l
Streptococcus pneumoniae	2 mg/l*	2 mg/l*
Haemophilus influenza	S ≤ 0.06 mg/l	R > 0.06 mg/l
Moraxella catarrhalis	S ≤ 0.5 mg/l	R > 0.5 mg/l
Pseudomonas species	S ≤ 0.5 mg/l	R > 0.5 mg/l

* Epidemiological cut-off value (ECOFF) for topical agents

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.

The following tables show the cases whose resistance patterns are known to vary in the European Union:

Acute Otitis Media with Tympanostomy Tubes (AOMT)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms: *Staphylococcus aureus* (methicillin-susceptible) *Streptococcus pneumoniae* Aerobic Gram negative micro organisms: *Haemophilus influenzae*

Moraxella catarrhalis *Pseudomonas aeruginosa*
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms: *Staphylococcus aureus* (methicillin-resistant)

Acute Otitis Externa (AOE)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms: *Staphylococcus aureus* (methicillin-susceptible) Aerobic Gram negative micro organisms: *Pseudomonas aeruginosa*
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms: *Staphylococcus aureus* (methicillin-resistant)

5.2 Pharmacokinetic properties

Auricular use

Blood samples were taken in two studies of AOMT to determine the plasma levels of ciprofloxacin and/or fluocinolone acetonide. Pharmacokinetic analysis showed no or negligible plasma level of the active ingredients demonstrating that topical application of Cetraxal Plus in the ear is unlikely to result in pharmacokinetically or clinically relevant systemic levels of ciprofloxacin and/or fluocinolone acetonide.

5.3 Preclinical safety data

The toxicity of ciprofloxacin has been deeply studied. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Adverse effects on the central nervous system and potential to damage cartilage as well as tendons have been described in human and preclinical studies. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed. However, these toxic effects have been observed after oral or IV administration at doses that cannot be achieved after otic administration.

Non-clinical data reveal low potential ototoxicity and systemic toxicity after intratympanic administration of the combination fluocinolone acetonide 0.025% plus ciprofloxacin 0.3%. The ototopical use of this product should be considered safe and no risk for hearing loss should be expected with its clinical use.

Fluocinolone acetonide was not genotoxic in the usual battery of genotoxicity tests.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of fluocinolone acetonide.

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 but there are no adequate and well-controlled reproductive and developmental toxicity studies with fluocinolone acetonide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80
Glycerin
Povidone
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

Shelf-life after first opening of the pouch: 7 days.

6.4 Special precautions for storage

Store below 30ºC. Store the single-dose containers in the pouch in order to protect from light.
After first opening of the single-dose container: use immediately and discard the single-dose container after use.

6.5 Nature and contents of container

The solution is contained within a formed low-density polyethylene (LDPE) single-dose container. Each single-dose container delivers 0.25 ml.
The single-dose containers are contained in an aluminium foil overwrap pouch for protection. Each pack contains 15 single-dose containers.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31.01.2018

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS Agency (link)}