Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciloxan 3 mg/ml ear drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 3mg ciprofloxacin as ciprofloxacin hydrochloride.
Excipient(s) with known effect: One ml of solution contains 0.06mg benzalkonium chloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ear drops, solution.
Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults and Children 1 year and above

CILOXAN is indicated for acute otitis externa due to susceptible strains of bacterial species shown to be responsive to ciprofloxacin as listed in section 5.1.

Use should be under the supervision of a specialist ENT service having the facilities for regular monitoring of clinical and microbiological effects during and after administration.

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

4.2 Posology and method of administration

Adults and children 1 year and above:

The dose is 4 drops of CILOXAN in the ear canal twice daily for adults.
For patients requiring use of an otowick, the dose can be doubled for the first administration only (i.e., 6 drops for paediatric patients and 8 drops for adult patients).

Use in elderly

No dosage alteration in elderly patients is necessary .
In clinical studies conducted with CILOXAN, the probability of having an adverse reaction was independent of age. No difference in patients experiencing adverse reactions was noted in
patients less than 65 years of age, between 65 and 75 years of age, and greater than 75 years of age.

Use in children
The dose is 3 drops of CILOXAN in the ear canal twice daily for children. Safety and effectiveness of CILOXAN was determined in 139 children between the ages of one and 12 years. No
serious adverse events were reported in these patients.

Safety and effectiveness in children below 1 year of age have not been established.

Use in hepatic and renal impairment

CILOXAN has not been studied in patients with hepatic or renal impairment and is therefore not recommended in such patients.

Method of administration

The bottle should be shaken well before use.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

The user should be instructed to warm the bottle just before use by holding it in the palm of the hand for a few minutes to prevent any unpleasant sensation associated with the cold suspension coming into contact with the ear.

With head tilted, instil the drops into the affected ear. Keep the head tilted on its side for a round 5 minutes to enable the drops to penetrate into the external auditory canal. Repeat if
necessary in the other ear.

To prevent contamination of the dropper tip and solution, ca e must be taken not to touch the auricle or the external ear canal, and surrounding areas, or other surfaces with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

4.3 Contraindications

Hypersensitivity to ciprofloxacin, to other quinolones or any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

- For otic use only.

•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.

•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.

- 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 tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions. (See section 4.8)

- Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

•CILOXAN should be suspended immediately at the first appearance of a skin rash or any other sign of hypersensitivity reaction and medical advice should be sought.

- Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

- As with all antibacterial preparations prolonged use of Ciprofloxacin may result in overgrowth of non-susceptible organisms, including fungi. If super infection occurs, appropriate therapy should be initiated.

•Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. Therefore treatment with CILOXAN should be discontinued at the first sign of tendon inflammation. (See section 4.8)

• Benzalkonium chloride, used as a preservative in this medicine is an irritant, may cause skin reactions when used topically.

4.5 Interaction with other medicinal products and other forms of interactions

Specific drug interaction studies have not been conducted with otic ciprofloxacin.

However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, 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.Given the low systemic concentration of ciprofloxacin following otic administration of the product, drug interactions are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Fertility

Studies have not been performed to evaluate the effect of topical administration of CILOXAN on fertility. Oral administration in animals does not indicate direct harmful effects with respect
to fertility.

Pregnancy

No adequate and well-controlled studies were performed in pregnant women.

Animal studies conducted with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity (see section 5.3).
Systemic exposure to ciprofloxacin after topical use is expected to be low.
As a precautionary measure, it is preferable to avoid the use of CILOXAN during pregnancy, unless the therapeutic benefit is expected to outweigh the potential risk to the fetus.

Lactation

Oral ciprofloxacin has been reported in human breast milk after a single 500 - mg dose. It is not known whether ciprofloxacin is excreted in human milk following otic administration. A risk
to the suckling child cannot be excluded. Caution should, therefore, beexercised when CILOXAN is administered to a nursing mother (see section 5.3).

4.7 Effects on ability to drive and use machines

There are no known effects of CILOXAN on the ability to drive and use machines. It is unlikely to have an effect.

4.8 Undesirable effects

In clinical trials the most frequently reported adverse drug reactions were ear pruritus and otorrhoea occurring approximately in1% of patients.

The adverse reactions listed below are classified according to the following 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), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience.

System Organ Classification	**MedDRA Preferred Term (v. 15.0)**
Nervous system disorders	*Uncommon*: headache

Ear and labyrinth disorders	*Uncommon*: ear pain, ear congestion, otorrhoea, ear pruritus, tinnitus
Skin and subcutaneous tissue disorders	*Uncommon*: dermatitis
General disorders and administration site conditions	*Uncommon:* pyrexia

Description of selected adverse events
In otic use the ingredients rarely are sensitising. However as with any substance that is applied to the skin, an allergic reaction to any of the ingredients of the preparation can always occur.

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, tingling, pharyngeal or facial oedema, dyspnoea, urticaria, and itching.

Ruptures of the shoulder, hand, Achilles, 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 Achilles tendon. To date, clinical and post marketing data have not demonstrated a clear association between CILOXAN and musculoskeletal and connective tissue adverse reactions.

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

Moderate to severe phototoxicity has been observed in patients treated with systemic quinolones. Nevertheless, phototoxic reactions to ciprofloxacin are uncommon.

Paediatric population
Safety and efficacy of CILOXAN 3mg/ml ear drops was determined in 193 children between the ages of one and 12 years of age. No serious adverse drug reaction was reported in this group of patients.

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 HPRA Pharmacovigilance, Website: www.hpra.ie;

4.9 Overdose

No case of overdose has been reported. No data are available in humans regarding overdosage by accidental or deliberate ingestion. Due to the characteristics of this preparation no toxic effects are to be expected with an otic overdose of this product, or in the event of accidental ingestion of the contents of one bottle.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Otological; Anti infectives.
ATC Code: S02AA

Mechanisms of Action:
CILOXAN ear drops, solution contains the fluoroquinolone ciprofloxacin. The cidal and inhibitory activity of ciprofloxacin against bacteria results from an interference with the DNA gyrase, an enzyme needed by the bacterium for the synthesis of DNA. Thus the vital information from the bacterial chromosomes cannot be transcribed any longer which causes a breakdown of the bacterial metabolism. Ciprofloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative micro - organisms: anaerobes are less susceptible.

Mechanism of Resistance
Fluoroquinolone resistance, particularly ciprofloxacin, requires significant genetic changes in one or more of five major bacterial mechanisms: a) enzymes for DNA synthesis, b) protecting
proteins, c) cell permeability, d) drug efflux, and e) plasmid - mediated amino glycoside 6'- N -acetyltransferase, AA C (6') - I b.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from amino glycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim, and chloramphenicol. Therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

Breakpoints
There are no official topical otic breakpoints for ciprofloxacin and although systemic breakpoints have been used, the irrelevance to topical otic therapy is doubtful. The EUCAST clinical MIC breakpoints used for this antibiotic are the following:

Staphylococcus species S ≤ 1mg /l , R ≥ 1mg /l
Pseudomonas aeruginosa S ≤ 0.5mg /l , R ≥ 1mg /l.

Susceptibility to Ciprofloxacin
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.

Commonly susceptible species
Aerobic Gram-positive micro-organisms:
Staphylococcus aureus (methicillin-susceptible; MSSA)
Aerobic Gram-negative micro-organisms:
Pseudomonas aeruginosa
Other micro-organisms:
None

Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms:
Staphylococcus aureus
Aerobic Gram-negative micro-organisms:
None
Other micro-organisms:
None

Inherently resistant organisms
Aerobic Gram-positive micro-organisms:
None
Aerobic Gram-negative micro-organisms:
None
Other micro-organisms:
None

5.2 Pharmacokinetic properties

The systemic pharmacokinetic properties of ciprofloxacin have been well studied. Ciprofloxacin widely distributes to tissues of the body, with tissue levels typically greater than levels in plasma. The apparent volume of distribution at steady state is 1.7-2.7 l/kg. Serum protein binding is 16-43%. The half-life of ciprofloxacin in serum is 3-5 hours. Following oral administration of single doses ranging from 250 to 750 mg to adults with normal renal function, 15-50% of the dose is excreted in urine as unchanged drug and 10-15% as metabolites within 24 hours. Both ciprofloxacin and its four primary metabolites are excreted in urine and faeces. Renal clearance of ciprofloxacin is typically 300-479 ml/minute. Approximately 20-40% of the dose is excreted in faeces as unchanged drug and metabolites within 5 days.

In children with otitis media with tympanostomy tubes treated with ciprofloxacin 3mg/ml solution (3 drops three times daily for 14 days), plasma concentrations of ciprofloxacin were not detected (limit of quantification 5ng/ml). In children with suppurative otitis with perforated tympanic membrane, treated by ciprofloxacin 2mg/ml solution (twice daily for 7-10 days), no circulating

plasma concentration of ciprofloxacin up to the limit of quantification 5ng/ml was detected. No significant systemic passage of ciprofloxacin is expected under the normal conditions of use.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical
developmental toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium acetate (trihydrate) (E262)
Acetic acid (E260)
Mannitol (E421)
Disodium edetate
Hydrochloric acid/sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years
Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not refrigerate or freeze

6.5 Nature and contents of container

Low-density polyethylene bottle and polypropylene screw cap.
Content: 5 ml

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
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8 MARKETING AUTHORISATION NUMBER

PA0896/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 2006

Date of last renewal: 03 February 2011

10 DATE OF REVISION OF THE TEXT

September 2020