SUMMARY PRODUCT CHARACTERISTICS (SPC)

CIPROFLOXACIN EYE/EAR DROPS (Ivyzoxan eye/ear drops)

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1. NAME OF MEDICINAL PRODUCT:

CIPROFLOXACIN EYE/EAR DROPS (Ivyzoxan eye/ear drops)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative composition:

Ciprofloxacin (as ciprofloxacin hydrochloride) USP

Quantitative composition:

Ciprofloxacin (as ciprofloxacin hydrochloride) 0.3% $^{w}/_{v}$. 3 mg/ml

For full list of Excipients, see section 6.1

3. PHARMACEUTICAL FORM OF THE DRUG PRODUCT

EYE/EAR DROP
5ml clear colourless solution

4. CLINICAL PARTICULARS

4.1 INDICATIONS

Adults and Children 1 year and above
Ivyzoxan Eye/Ear Drops is indicated for acute otitis externa due to susceptible strains of bacterial species shown to be responsive to ciprofloxacin.
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 Ivyzoxan Eye/Ear drops 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.

Use in children
The dose is 3 drops of Ivyzoxan Eye/Ear Drops in the ear canal twice daily for children. To prevent contamination of the dropper tip and solution, care 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.

4.3 Contraindications:

Hypersensitivity to ciprofloxacin, to other quinolones or any of the excipients

4.4 Special warnings and pre cautions for use:
• 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.
• 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.
• Ivyzoxan Eye/Ear Drops 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 Ivyzoxan Eye/Ear Drops should be discontinued at the first sign of tendon inflammation.
• Benzalkonium chloride, used as a preservative in this medicine is an irritant, may cause skin reactions when used topically.

4.5 Interactions 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 Pregnancy and lactation

Pregnancy
No adequate and well-controlled studies have performed in pregnant women. Animal studies conducted with ciprofloxacin do not indicate direct harmful effects with respect to reproductive toxicity.
Systemic exposure to ciprofloxacin after topical use is expected to be low.
As a precautionary measure, it is preferable to avoid the use of Ivyzoxan Eye/Ear Drops during pregnancy, unless the therapeutic benefit is expected to outweigh the potential risk to the fetus.

Women of child-bearing potential
No special recommendations for women of childbearing potential.

Lactation
Oral ciprofloxacin has been reported in human breast milk after a single 500-mg dose. It is not known whether topically applied ciprofloxacin is excreted in human milk. Caution should, therefore, be exercised when Ivyzoxan Eye/Ear Drops is administered to a nursing mother.

Fertility
Studies have not been performed to evaluate the effect of topical administration of Ivyzoxan Eye/Ear Drops on fertility.

Effects on ability to drive and use machines
There are no known effects of Ivyzoxan Eye/Ear Drops on the ability to drive and use machines. It is unlikely to have an effect.

4.8 Undesirable effects

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 reaction 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. 12.0)**
Nervous system disorders	*Uncommon*: crying, 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

In otic use the ingredients rarely are sensitizing. 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 acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.

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 Ivyzoxan Eye/Ear Drops 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.

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

Mechanisms of Action:

Ivyzoxan Eye/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 aminoglycoside 6'-N-acetyltransferase, AAC (6')-Ib.

Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, 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, their relevance 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: None 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

Reproduction studies have been performed in rats and mice at 100 mg/kg ciprofloxacin (900 times the proposed otic dose if a 10 kg child is treated with 0.27 mg of ciprofloxacin into each ear twice a day) and have revealed no evidence of impaired fertility or harm to the foetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg oral) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. It is known that orally administered ciprofloxacin is excreted in the milk of lactating rats.

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 30mg/kg ciprofloxacin the effect on joint was minimal. The dose is greater than 270 times the proposed otic clinical dose if a 10-kg child is treated with 0.27 mg ciprofloxacin into each ear twice a day.
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.

Fertility studies conducted in rats at oral doses of ciprofloxacin up to 100 mg/kg did not reveal any evidence of impairment.

Repeated-dose toxicological studies in rats and mice showed no evidence of tumorigenicity or carcinogenicity.

No carcinogenic or tumorigenic effects due to ciprofloxacin were observed during long-term carcinogenicity studies employing daily oral doses up to 250 and 750 mg/kg to rats and mice, respectively.

The mutagenic potential of ciprofloxacin has been studied using eight in vitro and three in vivo investigations. Six in vitro tests were negative while two were positive. However, the results of the three in vivo tests were negative. Thus there is no reason to suspect that ciprofloxacin has a mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Name of ingredient	**Reference**	**Amount per ml**	**Function/Reason For inclusion.**
Disodium edetate	BP	1mg	Chelating agent
Sodium chloride	BP	8mg	Tonicity adjusting agent
Benzalkonium chloride	BP	0.1mg	Preservative
Water for injection	BP	Quantity Sufficient to volume	Solvent

6.2 Incompatibilities

No significant incompatibility has been noted. Consult your physician, pharmacist or manufacturer incase incompatibility is suspected.

6.3 Shelf life:

Unopened shelf-life is 24 months.

Opened shelf-life 28 days.

But the patient is advised to discard any remaining drops after the prescribed course of treatment.

6.4 Special precautions for storage:

Store in a cool place (store below 25° C) away from light. Keep out of reach of children

6.5 Nature and contents of container:

5ml low density polyethylene bottles with a polypropylene spiked cap.

6.6 Special precautions for use and disposal:

No special requirement

7 MARKETING AUTHORISATION HOLDER

(Company) Name: **IVEE AQUA EPZ LTD.**

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8 MARKETING AUTHORISATION NUMBER

Registration number: 04-5049

9 DATE OF FIRST REGISTRATION/ RENEWAL OF REGISTRATION

1999

10 DATE OF REVISION OF TEXT

November 2020-11-25

11 DOSIMETRY (IF APPLICABLE) Not Applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUICALS (IF APPLICABLE) Not applicable