SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin 5mg/ml Eye Drops Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of eye drops, solution, contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg of levofloxacin.

Excipient with known effect:

One ml of eye drops, solution contains 0.05 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, pale yellow to pale greenish-yellow solution, practically free from visible particles.

The pH of the solution is 6.0-6.8 and the osmolality is 270-320 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levofloxacin 5 mg/ml eye drops are indicated for the topical treatment of bacterial external ocular infections in patients ≥1 year of age caused by levofloxacin susceptible microorganisms (see also sections 4.4 and 5.1).

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

Levofloxacin is indicated in adults, children aged ≥1 to 12 years and adolescents aged 12 to 18 years.

4.2 Posology and method of administration

Posology

For all patients instil one to two drops in the affected eye(s) every two hours up to 8 times per day while awake for the first two days and then four times daily on days 3 through 5.

If different topical ocular medications are used concomitantly, at least a 15-minute interval is required between instillations.

To prevent contaminating the dropper tip and solution, the dropper tip should not come into contact with the eyelids or surrounding areas.

The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection. The usual treatment duration is 5 days.

Safety and efficacy in the treatment of corneal ulcer and ophthalmia neonatorum has not been established.

Levofloxacin is not recommended for use in children below age 1 year due to a lack of data on safety and efficacy.

Use in the elderly

No adjustment of dosage is required.

Paediatric population

The posology is the same in adults and children aged ≥1 year.

The safety and efficacy of Levofloxacin in children aged ≥1 year have been established.

The safety and efficacy of Levofloxacin in children aged < 1 year have not yet been established. No data are available.

Method of administration

Ocular use.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones or to any of the excipients listed in section 6.1, e.g. benzalkonium chloride.

4.4 Special warnings and precautions for use

Levofloxacin 5 mg/ml eye drops must not be injected sub-conjunctivally. The solution should not be introduced directly into the anterior chamber of the eye.

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If worsening of infection occurs, or if a clinical improvement is not noted within a reasonable period, discontinue use and institute alternative therapy. Whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Systemic fluoroquinolones have been associated with hypersensitivity reactions, even following a single dose. If an allergic reaction to levofloxacin occurs, discontinue the medication.

Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including levofloxacin, particularly in older patients and those treated concurrently with corticosteroids. Therefore, caution should be exercised and treatment with Levofloxacin 5 mg/ml eye drops should be discontinued at the first sign of tendon inflammation (see section 4.8).

Patients with external bacterial ocular infections should not wear contact lenses.

Paediatric population
The special warnings and precautions for use are the same for adults and children aged ≥1 year.

Excipients
Levofloxacin 5 mg/ml eye drops contain benzalkonium chloride, which may be absorbed by soft contact lenses and may change the colour of the contact lenses. Contact lenses should be removed before using this medicine and may be put back in 15 minutes afterwards.

From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with levofloxacin eye drops.

Since maximum plasma concentrations of levofloxacin after ocular administration are at least 1000 times lower than those reported after standard oral doses, interactions mentioned for systemic use are unlikely to be clinically relevant when using Levofloxacin 5 mg/ml eye drops.

Paediatric population

No interaction studies have been performed.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Levofloxacin 5 mg/ml eye drops should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

Levofloxacin is excreted in human milk. However, at therapeutic doses of Levofloxacin no effects on the suckling child are anticipated. Levofloxacin 5 mg/ml eye drops should be used during lactation only if the potential benefit justifies any potential risk to the nursing child.

Fertility

Levofloxacin caused no impairment of fertility in rats at exposures considerably in excess of the maximum human exposure after ocular administration (see section 5.3).

4.7 Effects on ability to drive and use machines

Levofloxacin has minor influence on the ability to drive and use machines.

If there are any transient effects on vision, the patient should be advised to wait until this clears before driving or operating machinery.

4.8 Undesirable effects

Approximately 10 % of patients can be expected to experience adverse reactions. The reactions are usually graded as mild or moderate, are transient, and are generally restricted to the eye.

As the product contains benzalkonium chloride, contact eczema and/or irritation may be due to the active component or to this preservative.

The following undesirable effects assessed as definitely, probably or possibly related to treatment were reported during clinical trials and post-marketing experience with levofloxacin containing eye drops:

Frequency categories are expressed as: *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):

Immune system disorders
Rare: Extra-ocular allergic reactions, including skin rash
Very rare: Anaphylaxis

Nervous system disorders
Uncommon: Headache

Eye disorders
Common: Ocular burning, decreased vision and mucous strand.
Uncommon: Lid matting, chemosis, conjunctival papillary reaction, lid oedema, ocular discomfort, ocular itching, ocular pain, conjunctival injection, conjunctival follicles, ocular dryness, lid erythema, and photophobia.

No corneal precipitates were observed in clinical studies.

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis
Very rare: Laryngeal oedema

Additional adverse reactions that have been seen with the systemic use of the active substance (levofloxacin), and may potentially occur also with Levofloxacin 5mg/ml eye drops

Musculoskeletal and connective tissue disorders
Rare: 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 quinolones indicate that a risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including Achilles tendon (see section 4.4).

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The total amount of levofloxacin in a bottle of eye drops is too small to induce toxic effects after an accidental oral intake. If considered necessary, the patient can be observed clinically and supportive measures can be undertaken. After a local overdose with Levofloxacin 5 mg/ml eye drops, the eyes can be flushed with clean (tap) water at room temperature.

Paediatric population

Actions to be taken in case of overdose are the same in adults and in children aged ≥1 year.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinfectives, fluoroquinolones, ATC code: S01AE05.

Levofloxacin is the L-isomer of the racemic drug substance ofloxacin. The antibacterial activity of ofloxacin resides primarily in the L-isomer.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin inhibits bacterial type II topoisomerases—DNA gyrase and topoisomerase IV. Levofloxacin preferentially targets DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria.

Mechanisms of resistance

Bacterial resistance to levofloxacin can develop primarily due to two main mechanisms, namely a decrease in the intrabacterial concentration of a drug, or alterations in a drug's target enzymes. Target site alteration results from mutations in the chromosomal genes encoding the DNA gyrase (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*; *grlA* and *grlB* in *Staphylococcus aureus*). Resistance due to low intrabacterial drug concentration follows either from altered outer-membrane porins (OmpF) leading to reduced entry of fluoroquinolones in Gram-negative bacteria or from efflux pumps. Efflux- mediated resistance has been described in pneumococci (PmrA), staphylococci (NorA), anaerobes, and Gram-

negative bacteria. Finally, plasmid-mediated resistance to quinolones (determined by the *qnr* gene) has been reported in *Klebsiella pneumoniae* and in *E. coli*.

Cross-resistance

Cross-resistance between fluoroquinolones may occur. Single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the fluoroquinolone class. Altered outer- membrane porins and efflux systems may have a broad substrate specificity, targeting several classes of antibacterial agents and leading to multiresistance.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for levofloxacin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Paediatric population

Pharmacodynamic properties are the same in adults and children aged ≥1 year.

5.2 Pharmacokinetic properties

After ocular instillation, levofloxacin is well maintained in the tear-film.

In a healthy-volunteer study, mean tear-film concentrations of levofloxacin measured four and six hours after topical dosing were 17.0 and 6.6 µg/mL, respectively. Five of six subjects studied had concentrations of 2 µg/mL or above at 4 hours post dose. Four of the six subjects maintained this concentration at 6 hours post dose.

Levofloxacin concentration in plasma was measured in 15 healthy adult volunteers at various time points during a 15-day course of treatment with levofloxacin 5 mg/ml eye drops solution. The mean levofloxacin concentration in plasma 1 hour post-dose ranged from 0.86 ng/mL on Day 1 to 2.05 ng/mL on Day 15. The highest maximum levofloxacin concentration of 2.25 ng/mL was measured on Day 4 following 2 days of dosing every 2 hours for a total of 8 doses per day. Maximum levofloxacin concentrations increased from 0.94 ng/mL on Day 1 to 2.15 ng/mL on Day 15, which is more than 1000 times lower than those reported after standard oral doses of levofloxacin.

As yet, the plasma concentrations of levofloxacin reached after application to infected eyes are not known.

5.3 Preclinical safety data

Preclinical effects were observed only at exposures considerably in excess of the maximum human exposure after instillation of levofloxacin 5 mg/ml eye drops, indicating little relevance to clinical use.

Gyrase inhibitors have been shown to cause growth disorders of weight bearing joints in animal studies.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs after high oral doses.

A cataractogenic potential cannot be ruled out due to the lack of specific investigations.

Visual disorders in animals cannot be ruled out with certainty on the basis of the present data.

Reproductive toxicity:

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day. Since levofloxacin has been shown to be completely absorbed, the kinetics are linear. No differences were noted in the pharmacokinetic parameters between single and multiple oral doses. Systemic exposure in rats dosed at 810 mg/kg/day is approximately 50,000 times greater than that achieved in humans after doses of 2 drops of levofloxacin 5 mg/ml eye drops to both eyes. In rats the highest dose caused increased foetal mortality and delayed maturation coincident with maternal toxicity. No teratogenic effect was observed when rabbits were dosed orally with up to 50 mg/kg/day or when dosed intravenously as high as 25 mg/kg/day. Levofloxacin caused no impairment of fertility in rats at oral doses as high as 360 mg/kg/day, resulting in approximately 16,000 times higher plasma concentrations than reached after 8 ocular doses in humans.

Genotoxicity:

Levofloxacin did not induce gene mutations in bacterial or mammalian cells, but did induce chromosome aberrations in Chinese hamster lung (CHL) cells *in vitro* at or above 100 µg/mL in the absence of metabolic activation. *In-vivo* tests did not show any genotoxic potential.

Phototoxic potential:

Studies in the mouse after both oral and intravenous dosing showed levofloxacin to have phototoxic activity only at very high doses. Neither cutaneous photosensitising potential nor skin phototoxic potential were observed after application of a 3 % ophthalmic solution of levofloxacin to the shaven skin of guinea pigs. Levofloxacin

did not show any genotoxic potential in a photomutagenic assay, and it reduced tumour development in a photocarcinogenicity assay.

Carcinogenic potential:

In a long-term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumorigenic potential following daily dietary administration of up to 100 mg/kg/day for 2 years.

Environmental Risk Assessment (ERA)

The calculated predicted environmental concentration ($PEC_{Surfacewater}$) for levofloxacin 5 mg/ml eye drops is below the action limit 0.01 µg/l and levofloxacin LogKow-value is below action limit 4.5. It is highly unlikely that levofloxacin 5 mg/ml eye drops would represent a risk to the environment because no other environmental concerns are apparent for this product and its active substance levofloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride (0.05 mg in 1 ml eye drops, solution)

Sodium chloride

Sodium hydroxide or hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened bottle: 3 years.

After first opening the bottle: 4 weeks.

6.4 Special precautions for storage

Unopened bottle: This medicinal product does not require any special storage conditions.

Opened bottle: Do not store above 25°C. Keep bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

White LDPE 5 ml bottle with a white LDPE dropper and a white high density polyethylene (HDPE)/ LDPE tamper-evident seal cap.

Pack size: one bottle in a cardboard box.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
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Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0946

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/11/2025

10 DATE OF REVISION OF THE TEXT

24/11/2025