

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Product name 5 mg/ml eye drops solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of eye drops, solution, contains 5.12 mg levofloxacin hemihydrate equivalent to 5.0 mg of levofloxacin.

For the theoretical volume of one drop equivalent to 0.05ml, the amount of drug substance is 0.256mg levofloxacin hemihydrate equivalent to 0.250 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 green yellowish aqueous solution

Isotonic solution adjusted to physiological pH-value range.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Product name 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).

Product name 5 mg/ml is indicated in adults, children aged ≥ 1 to 12 years and adolescents aged 12 to 18 years.

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

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.

Product name 5 mg/ml is not recommended for use in children below age 1 year due to a lack of data on safety and efficacy.

Paediatric population

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

The safety and efficacy of Levofloxacin 5 mg/ml in children aged ≥ 1 year have been established.

The safety and efficacy of Levofloxacin 5 mg/ml in children < 1 year has not yet been established.

No data are available.

Use in the Elderly

No adjustment of dosage is required.

Method of administration

Ocular use.

4.3 Contraindications

Hypersensitivity to the active substance levofloxacin, 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

Product name eye drops must not be injected sub-conjunctivally. The solution should not be introduced directly into the anterior chamber of the eye.

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 **Product name** should be discontinued at the first sign of tendon inflammation (see section 4.8).

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.

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

Product name eye drops contain benzalkonium chloride, which may cause eye irritation.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with **Product name** 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. If different topical ocular medications are used concomitantly, at least a 15-minute interval is required between instillations.

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.

Product name 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. **Product name** 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

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

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 5 mg/ml eye drops.

System organ Class	Frequency	Adverse reaction
<i>Immune system disorders</i>	Rare	Extra-ocular allergic reactions, including skin rash
	Very rare, not known (cannot be estimated from the available data)	Anaphylaxis.
<i>Nervous system disorders</i>	Uncommon	Headache
<i>Eye disorders</i>	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.
<i>Respiratory, thoracic and mediastinal disorders</i>	Uncommon	Rhinitis
	Very rare, not known (cannot be estimated from the available data)	Laryngeal oedema

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 national reporting system listed in Appendix V***.

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 **Product name** 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 Levofloxacin resides primarily in the L-isomer.

Mode 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 intra-bacterial concentration of a drug, or alterations in 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.

Break points

MIC breakpoints separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms according to breakpoint of EUCAST (European Committee on Antimicrobial Susceptibility Testing) are as follows:

Pseudomonas spp., *Staphylococcus* spp., *Streptococcus* A,B,C,G:

Susceptible ≤ 1mg/L, resistant > 2mg/L

Streptococcus pneumoniae: Susceptible ≤ 2mg/L, resistant > 2mg/L

Haemophilus influenzae, *Moraxella catarrhalis*: Susceptible ≤ 1mg/L, resistant > 1mg/L

All other pathogens: Susceptible ≤ 1mg/L, resistant > 2mg/L

Antibacterial spectrum

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. Therefore the information presented provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to levofloxacin or not. 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.

Only those bacterial species that are commonly responsible for external ocular infections, such as conjunctivitis, are presented here in the following table.

Antibacterial spectrum – susceptibility category and resistance characteristics according to EUCAST

Category I: Commonly susceptible species	
Aerobic Gram-positive micro-organisms	
<i>Staphylococcus aureus</i> (MSSA)*	
<i>Streptococcus pneumoniae</i>	
<i>Streptococcus pyogenes</i>	
Viridans group of streptococci	
Aerobic Gram-negative micro-organisms	
<i>Escherichia coli</i>	
<i>Haemophilus influenzae</i>	
<i>Moraxella catarrhalis</i>	
<i>Pseudomonas aeruginosa</i>	(Community isolates)

Other micro-organisms	
<i>Chlamydia trachomatis</i>	(Treatment of patients with chlamydial conjunctivitis requires concomitant systemic antimicrobial treatment)
Category II: Species for which acquired resistance may be a problem	
Aerobic Gram-positive micro-organisms	
<i>Staphylococcus aureus</i> (MRSA)**	
<i>Staphylococcus epidermidis</i>	
Aerobic Gram-negative micro-organisms	
<i>Pseudomonas aeruginosa</i>	(Hospital isolates)

* MSSA = methicillin-susceptible strains of *Staphylococcus aureus*

** MRSA = methicillin-resistant strains of *Staphylococcus aureus*

Resistance data presented in the table are based on the results of a multicentre surveillance study (Ophthalmic Study) on the prevalence of resistance among bacterial isolates obtained from patients with eye infections in Germany, June – November 2004.

Organisms have been classified as levofloxacin-susceptible based on in-vitro susceptibility and plasma concentrations reached after systemic therapy. Topical therapy achieves higher peak concentrations than found in plasma. However, it is not known if or how the kinetics of the drug after topical application to the eye may modify the antibacterial activity of levofloxacin.

Paediatric population

Pharmacodynamics 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 $\mu\text{g/mL}$, respectively. Five of six subjects studied had concentrations of 2 $\mu\text{g/mL}$ 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 fetal 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,
Water for Injections.
NaOH / or HCL (for pH-adjustment).

6.2 Incompatibilities

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

6.3 Shelf life

3 years.
After first opening: to be used within 28 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 ml Low-Density Polyethylene (LDPE) sterile bottle, with tamper-proof evident, with a LDPE dropper tip and a HDPE (high-density polyethylene) or HDPE/ LDPE screw caps.

Pack sizes: 1 bottle x 5 ml

6.6 Special precautions for disposal and other handling

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

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>