SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levofloxan 5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains: 5 mg levofloxacin (as levofloxacin hemihydrate)

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Levofloxan 5 mg/ml eye drops is 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).

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

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

Levofloxan 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.

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

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.

Levofloxan 5 mg/ml eye drops contains benzalkonium chloride, which may cause eye irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been conducted with Levofloxan 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 Levofloxan 5 mg/ml eye drops.

If simultaneously using other ophthalmic drugs for topical application, it requires an interval of at least 15 minutes between the two applications.

4.6 Fertility, pregnancy and lactation

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).

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. Levofloxan 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 Levofloxan no effects on the suckling child are anticipated. Levofloxan 5 mg/ml eye drops should be used during lactation only if the potential benefit justifies any potential risk to the nursing child.

4.7 Effects on ability to drive and use machines

Levofloxan eye drops 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 Levofloxan eye drops:

Eye disorders
Common (>1/100, <1/10): Ocular burning, decreased vision and mucous strand.
Uncommon (>1/1,000, <1/100): Lid matting, chemosis, conjunctival papillary reaction, lid oedema, ocular discomfort, ocular itching, ocular pain, conjunctival injection, conjunctival follicles, ocular dryness, lid erythema, and photophobia.

In clinical trials, no precipitations are observed in the cornea.

Immune system disorders
Rare (>1/10,000, <1/1,000): extra-ocular allergic reactions, including skin rash.
Very rare (< 1/10,000), not known (cannot be estimated from the available data): anaphylaxis

Nervous system disorders
Uncommon (>1/1,000, <1/100): headache.

Respiratory, thoracic and mediastinal disorders
Uncommon (>1/1,000, <1/100): rhinitis.
Very rare (< 1/10,000), not known (cannot be estimated from the available data): Laryngeal oedema.

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.

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 Levofloxan 5 mg/ml eye drops, the eyes can be flushed with clean (tap) water at room temperature.

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.

Breakpoints

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 < 1 mg/L, resistant > 2 mg/L

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

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

All other pathogens: Susceptible < 1 mg/L, resistant > 2 mg/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
Staphylococcus aureus (MSSA)*
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci
Aerobic Gram-negative micro-organisms
Escherichia coli
Haemophilus influenzae

Moraxella catarrhalis	
Pseudomonas aeruginosa	(Community isolates)
Other micro-organisms	
Chlamydia trachomatis	(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	
Staphylococcus aureus (MRSA)**	
Staphylococcus epidermidis	
Aerobic Gram-negative micro-organisms	
Pseudomonas aeruginosa	(Hospital isolates)

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

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.

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 Levofloxan 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 Levofloxan 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 is 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 Levofloxan 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (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

3 (three) years.
After first opening: to be used within 28 days at a temperature not above 25°C.

6.4 Special precautions for storage

Do not store above 25°C
Do not freeze.
Keep the container tightly closed.

6.5 Nature and contents of container

White plastic vials.
One vial per carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

8 MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

January 2015