# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Oftaquix Unit Dose 5 mg/ml eye drops, solution in single-dose container

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of eye drops, solution, contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg of levofloxacin.
One single-dose container (0.3 ml) contains 1.5 mg of levofloxacin.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Eye drops, solution in single-dose container.
Clear, light yellow to light greenish-yellow solution, practically free of visible particulate matter.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Oftaquix Unit Dose 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).

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

Oftaquix Unit Dose 5 mg/ml eye drops are indicated in adults, children aged ≥1 year 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.

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

Method of administration
Ocular use.
For single use only.

The contents of one single-dose container are sufficient for both eyes.
The eye drops, solution should be used immediately after first opening the single dose container.
The used single dose container should be discarded.

## 4.3 Contraindications

Hypersensitivity to the active substance levofloxacin, to other quinolones or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Oftaquix 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.

Patients with external bacterial ocular infections should not wear contact lenses.
Oftaquix 5 mg/ml eye drops contain benzalkonium chloride, which may cause eye irritation.

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

Paediatric population

The special warnings and precautions for use are the same in 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 Oftaquix Unit Dose 5 mg/ml 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 Oftaquix Unit Dose 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. Oftaquix Unit Dose 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 Oftaquix no effects on the suckling child are anticipated. Oftaquix Unit Dose 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

Oftaquix Unit Dose 5 mg/ml eye drops have 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.

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 (Oftaquix 5 mg/ml eye drops and Oftaquix Unit Dose 5 mg/ml eye drops in single-dose container):

*Immune system disorders*
Rare (≥1/10,000 to <1/1,000): Extra-ocular allergic reactions, including skin rash.
Very rare (<1/10,000): Anaphylaxis.

*Nervous system disorders*
Uncommon (≥1/1,000 to <1/100): Headache.

*Eye disorders*
Common (≥1/100 to <1/10): Ocular burning, decreased vision and mucous strand.

Uncommon (≥1/1,000 to <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.
No corneal precipitates were observed in clinical studies.

*Respiratory, thoracic and mediastinal disorders*
Uncommon (≥1/1,000 to <1/100): Rhinitis.
Very rare (<1/10,000): Laryngeal oedema.

*Additional adverse reactions that have been seen with the systemic use of the active substance (levofloxacin), and may potentially occur also with Oftaquix:*
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).

<u>Paediatric population</u>
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 at: 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 the provided amount of single-dose container 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 Oftaquix Unit Dose 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.

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*

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
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 (Oftaquix 5 mg/ml eye drops in multi dose container preserved with benzalkonium chloride) 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 six subjects maintained this concentration at 6 hours post dose.

The penetration of topically applied Oftaquix 5 mg/ml in multi dose container and ofloxacin 3 mg/ml eye drops into the aqueous humour of 35 patients undergoing cataract surgery was investigated. One drop of either drug was administered four times into the eye to be operated (1 hour, 45 min, 30 min and 15 min before the operation). The mean concentration of levofloxacin of Oftaquix in the aqueous humour was statistically significantly higher than that of ofloxacin (p=0.0008). In fact, it was approximately twice as high as that of ofloxacin (1139.9 ± 717.1 ng/ml vs. 621.7 ± 368.7 ng/ml).

Levofloxacin concentration in plasma was measured in 15 healthy adult volunteers at various time points during a 15-day course of treatment with Oftaquix 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 Oftaquix 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 Oftaquix 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 Oftaquix Unit Dose 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 Oftaquix Unit Dose 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

Sodium chloride

Diluted sodium hydroxide solution or diluted hydrochloric acid

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

2 years
After first opening the pouch: 3 months
Discard any unused single-dose container after that time.
After first use: Discard the opened single-dose container with any remaining solution immediately.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original pouch in order to protect from light.

### 6.5 Nature and contents of container

Low-density polyethylene (LDPE) single-dose containers.
Single-dose containers of strip of ten are packed in paper-coated, aluminium-polyethylene foil pouch.

Pack sizes: 10 x 0.3 ml, 20 x 0.3 ml, 30 x 0.3 ml and 60 x 0.3 ml.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 16058/0007

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/06/2011

## 10 DATE OF REVISION OF THE TEXT

21/05/2021