

LEVOFLOXACIN 5 MG/ML EYE DROPS

PL 16058/0009

UKPAR

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LEVOFLOXACIN 5 MG/ML EYE DROPS

PL 16058/0009

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Santen Oy a Marketing Authorisation (licence) for the medicinal product Levofloxacin 5 mg/ml eye drops (PL 16058/0009). This medicine is available by prescription only.

This antibiotic kills certain bacteria or stops their growth and can be used to treat bacterial eye infections.

Levofloxacin 5 mg/ml eye drops raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

LEVOFLOXACIN 5 MG/ML EYE DROPS

PL 16058/0009

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Levofloxacin 5 mg/ml eye drops (PL 16058/0009) on 21 June 2006. This product can only be obtained with a prescription.

This is a national application for Levofloxacin 5 mg/ml eye drops submitted under Article 8.3(i) of Directive 2001/83, as a duplicate of Oftaquix 5 mg/ml eye drops (PL 16058/0006), licenced to Santen Oy in the UK on 31 July 2001.

Levofloxacin 5 mg/ml eye drops contain the active ingredient levofloxacin hemihydrate, a fluoroquinolone antibiotic.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

This is a complete application for Marketing Authorisation in the UK submitted under Article 8.3(i) of Directive 2001/83 (as amended), for a known active substance. The application is a duplicate of Oftaquix 5 mg/ml eye drops (PL 16058/0006) which was approved in the UK on 31 July 2001, followed by mutual recognition procedure (UK/H/464/01) finalised on 5 March 2002.

A statement has been provided confirming that the application is a duplicate of PL 16058/006, with the inclusion of the variations since approval. The variations are three type I variations (UK/H/0464/01/V01, 02, 03) covering the tamper evidence of the containers and a change in the batch size of the product. There is also a type II variation (UK/H/0464/001/II/004) relating to the addition of an alternative start material in the manufacture of the active substance. Additional information has been provided including a correlation table for transfer to CTD format and descriptions of minor revisions.

Subsequent mutual recognition procedures are considered for this application.

2. ACTIVE SUBSTANCE

The active substance is manufactured at a suitable site. The active substance has a DMF and a letter of access has been provided for use with Levofloxacin 5 mg/ml eye drops (PL 16058/0009). The relevant applicant part has been included in module 3. The DMF has been assessed in relation to other products licensed in the UK, which includes the original licence. Full details of the variation to include the alternative start material have been included.

3. DRUG PRODUCT

Manufacture

Manufacturer

A manufacturer's licence has been included with the MAA. The manufacture of eye drops is covered by the licence. A certificate of GMP compliance has also been supplied by the relevant authorities, dated June 2004.

Batch formula

Batch formulas have been presented.

Process validation or evaluation

Validation has been performed on five batches. Samples were assessed at the beginning, middle and end of the production run to suitable specifications. All five batches were within specification and comparable across the five batches, demonstrating that the process used is reproducible. The related substances for all batches was either below the level of quantitation or not detected.

Microbiological status was assessed on the unsterilised bulk and the finished product. The results showed that no bioburden was detected and the finished product met the requirements of sterility at the beginning and end of filling.

The filter system has been satisfactorily validated. The challenge test exposed three filters from separate batches to simulated process filtered conditions for the whole filtration time and was then subjected to a bacterial challenge. All filters gave higher than the minimum acceptable bubble point values pre and post challenge. Complete retention of the microbe was demonstrated for the three filters.

It has been demonstrated that the filter has no effect on the chemical quality of the product. There is some initial adsorption of benzalkonium chloride on the filter, however this stabilises at about 4 litres, consequently the first part of the filtrate is discarded.

Validation of the aseptic filling process has been demonstrated. Media fill runs are completed twice a year.

Validation of the methods used for the sterilisation of the equipment have been included.

Control of drug product

Specification

The finished product specification for the product is satisfactory, with appropriate tests and limits listed.

Analytical procedures

All analytical procedures are satisfactory, including the test method for antimicrobial preservative effectiveness. The method is as described in the European Pharmacopoeia.

Validation

Data has been provided demonstrating that all methods have been validated.

Batch analyses

Batch analyses data has been updated with data provided for four batches. Certificates of analysis have not been provided. The analysis data is satisfactory.

Container closure system

There are now two different container configurations the difference being the method to confirm tamper evidence of the container. The two configurations are the ratchet ring and shrink banded. The shrink banded was added to the licence by variation.

The materials and specifications of the bottles, dropper tips and caps remain the same as the original application. The specifications, certificates and drawings have been supplied for the bottle, dropper and cap.

All materials used comply with the European Pharmacopoeia monograph for polyethylene without additives for containers for preparations for parental use or for ophthalmic preparations. The dose distribution was shown to be consistent and reproducible ranging from 25 to 40kGy.

Stability

Stability data has been supplied for the shrink banded presentation. At 25°C/40%RH the batches are at 24, 18 and 9 months respectively. Two of the batches have also completed 6 months at 40°C/≤25%RH. These were in the commercial presentation. The bottles were inverted for the stability.

All three batches are in specification for the data presented. There is a slight increase in assay and total impurities. This would be expected for a semi-permeable container. All batches remain in specification.

The ratchet ring data has been updated to 36 months, all batches meet the specifications. The inverted batches also comply with the tests for sterility and antimicrobial preservative effectiveness.

The stability report states that the product can be stored at or below 25°C for three years.

The stability data presented supports the shelf-life.

4. PRODUCT LITERATURE

SPC

The Summary of Product Characteristics is satisfactory.

PIL

The Patient Information Leaflet is satisfactory.

LABEL

All labelling is satisfactory.

5. ADMINISTRATIVE

MAA form

The Marketing Authorisation Application form is satisfactory.

Quality overall summary

The quality overall summary for the active substance has been completed by the General Manager of Quality Assurance at the drug substance manufacturing site, with the report being a summary of the active substance part of the module. The quality overall summary for the product has been completed by a suitably qualified expert, with the report being a summary of the pharmaceutical part of the module.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is national abridged standard application for marketing authorisation for Levofloxacin 5 mg/ml eye drops with benzalkonium preservative. It is submitted under EC Article 8.3(i) of Directive 2001/83 (as amended).

The product is a duplicate of the original Oftaquix (PL 16058/ 0006) 5 mg/ml eye drops, which contain 0.005% benzalkonium chloride (BAK) as a preservative. The original product was approved in the UK on 31 July 2001 and was followed by MRP UK/H/464/01, licensed on 5th March 2002.

This application is a complete and independent application but the same data package that was used as the basis of the MRP is used in this application. Letters of access have been provided.

A subsequent MRP is planned for this product.

2. BACKGROUND

Levofloxacin is the S-(-) optical isomer of ofloxacin and is a broad spectrum anti-infective compound, with similar physicochemical, pharmacological and toxicological properties to other marketed fluoroquinolones. It has been demonstrated in *in vivo* and *in vitro* studies to be up to four times more active than ofloxacin.

3. 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 micro-organisms (see also sections 4.4 and 5.1).

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

Assessor's comments

This is identical to the indications for the innovator product.

4. DOSE & DOSE SCHEDULE

For all patients instil one to two drops in the affected eye(s) every two hours up to eight 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.

While Levofloxacin 5 mg/ml eye drops have been administered for up to 15 days in a safety study, the usual treatment duration is 5 days.

The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection.

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

Use in the elderly

No adjustment of dosage is required.

Method of administration

Ocular use.

Assessor's comments

This was identical to the SPC for the innovator product Oftaquix 5 mg/ml eye drops solution at the time point of submission of application for PL 16058/0009.

5. TOXICOLOGY

The toxicological profile of levofloxacin has been well described. No new toxicological concerns are described and no new toxicological data is required.

6. CLINICAL PHARMACOLOGY

Pharmacokinetics

No dissolution, bioavailability, or bioequivalence studies have been performed, this is satisfactory for an application of this type.

Supportive Pharmacokinetics

As supportive evidence the company included pharmacokinetic studies previously submitted in the MRP application in this application dossier:

In Summary:

Two pharmacokinetic studies were submitted which measured the concentrations of levofloxacin achieved in the aqueous humor after application prior to cataract surgery of either preserved (Oftaquix 5mg/ml eye drops) conducted by Koch et al. (J Cataract Refract Surg 2005;31:1377-85) or unpreserved (Cravit ophthalmic solution, marketed by Santen in Japan) by Yamada et al. (Current Eye Research 2002;24:403-6).

Results

The concentration of levofloxacin in the aqueous humor was similar for the preserved and non-preserved formulations.

In addition, three further studies were described in the dossier: studies 03-005 and 03-006, measuring concentrations of levofloxacin eye drops with preservative in plasma and tears respectively; and study 95034, without preservative in plasma.

Results

Studies 03-005 and 03-006 using the preserved formulation demonstrated low measurable levels of levofloxacin in serum and levels above MIC₉₀ in the tear fluid for at least 6 hours respectively. In study 95034, using the unpreserved formulation levofloxacin was not detected in the serum. This latter result was at variance to study 03-005 but this was explained by the fact that the analytical technique used in this study had a level of detection of 10ng/mL, a value that exceeded the actual levels found in study 03-005.

Assessor's Comments on levofloxacin pharmacokinetics

The indication for Levofloxacin 5 mg/ml eye drops is for the topical treatment of extra-ocular infections. The product is an aqueous topical ophthalmic solution containing the same active substance, levofloxacin in the same concentration as the original cross-referral product, PL 16058/0006) Oftaquix 5 mg/ml Eye Drops.

The pharmacology of levofloxacin eye drops has been adequately demonstrated in the previous MRP application *MRP UK/H/464/01*. Therefore the pharmacokinetic studies submitted in the dossier and described above are superfluous to requirements in this application and are not directly relevant.

7. EFFICACY

The efficacy of the (preserved) Oftaquix 5mg/ml Eye Drops has already been established in the UK and MRP UK/H/464/01 applications for this product.

8. SAFETY

8.1

The original formulation of Oftaquix 5 mg/ml eye drops contained 0.005% of BAK as a preservative. This low concentration is regarded as safe. BAK is a surfactant used as a preservative in eye drops. It is preferred by many manufacturers because of its stability, excellent antimicrobial properties and long shelf-life. However, it also exhibits toxic effects on both the tear film and corneal epithelium. It has been shown that repeated use of preserved medications negatively affects the ocular surface, especially in patients whose ocular surface is compromised (Baudouin 1996). The usual dosage duration of the treatment Oftaquix 5 mg/ml eye drops is 5 days.

Adverse Effects

About 17 million patients have used preserved Oftaquix and Quixin in Europe and in the USA, respectively and unpreserved Cravit in Japan during the period from 1 August 2001 to 31 January, 2004. It has been generally well tolerated. Eleven serious adverse effects were reported in this time period. None of these led to a change in the reference safety information.

Several allergic reactions have been reported and the reference safety information has been changed accordingly.

8.2 PMS

A Periodic Safety Update Report for Oftaquix (levofloxacin hemihydrate) Eye Drops for the period from 1 August 2001 and 31 January 2004, is included in the submission dossier. This is the period from granting of the first marketing authorisation by the UK MCA (now the MHRA) on 31 July 2001.

Approximately 10% of patients can be expected to experience adverse reactions after topical treatment with Oftaquix. These reactions are usually mild to moderate, transient and generally restricted to the eye. The most frequently reported adverse reactions are ocular burning, decreased vision and mucous strand.

As with other fluoroquinolones, allergic reactions may occur in less than 1% of patients. Several allergic reactions have been reported during levofloxacin treatment.

The calculations of patient exposure are based on the sales data. A total of 199,000 units of Oftaquix were sold during the review period. The average patient exposure is estimated to be 5 days per bottle, the most commonly prescribed duration of treatment. An estimate of the patient exposure is therefore 199,000 patients.

During the review period, a total of 661,000 units of Oftaquix (Quixin in USA) were sold with the same duration of therapy and, therefore, the corresponding number of patients. In Japan, 47 million units of Cravit (unpreserved Oftaquix solution in multidose container) were sold and the average treatment duration was 20.4 days using 2.9 bottles per patient, therefore the estimated patient exposure is approximately 16.2 million. In total about 17 million patients have used Oftaquix (Quixin, USA and Cravit, Japan) during the review.

The PSUR reviews a number of spontaneous reports mostly from physicians directly. In general, Oftaquix 5 mg/ml eye drops have been well tolerated. Eleven serious adverse drug reactions were reported. It is known that 10 of these recovered and the outcome of the eleventh is unknown. None of them led to a change in the reference safety information. Several allergic reactions have been reported and the reference safety information has been changed accordingly.

Summary of Overall Clinical Safety.

See Section 8.1, above.

Medical Assessor's Comments on Safety

The safety of Oftaquix 5 mg/ml eye drops with the preservative BAK has been previously demonstrated in the MRP application *MRP UK/H/464/01*. This is supported by the PMS data and PSUR summarised in sections 8.1 and 8.2 above.

Eleven serious adverse drug reactions were reported. It is known that 10 of these recovered and the outcome of the eleventh is unknown. None of them led to a change in the reference safety information. Several allergic reactions have been reported and the reference safety information has been changed accordingly.

9. EXPERT REPORTS

The Clinical Overview consists of an introduction and the Clinical Expert Report, which was submitted in the MRP application MRP UK/H/464/0. This was written by a suitably qualified expert. This report reviews levofloxacin as an anti-infective for the eye and the pharmacological studies both with and without preservative and the clinical efficacy and safety studies conducted on Oftaquix 5mg/ml eye drops with preservative submitted previously for the MRP.

10. SUMMARY OF PRODUCT CHARACTERISTICS

This was identical to the MRP approved SmPC for Oftaquix 5 mg/ml eye drops with preservative at the time point of submission of application for PL 16058/0009.

11. PATIENT INFORMATION LEAFLET

This was identical to the approved PIL for Oftaquix 5 mg/ml eye drops with preservative at the time point of submission of application for PL 16058/0009.

12. LABELLING

This is essentially identical to the approved labelling for Oftaquix 5 mg/ml eye drops with preservative.

13. MAA

This is clinically satisfactory.

14. DISCUSSION

The dossier for this standard, national, abridged application for Levofloxacin 5 mg/ml eye drops demonstrated that the formulation is the same as the licensed Oftaquix 5 mg/ml eye drops.

Efficacy and safety for this formulation has previously been established. PMS data submitted supports the safety profile already established. Eleven serious adverse drug reactions were reported. It is known that 10 of these recovered and the outcome of the eleventh is unknown. None of them led to a change in the reference safety information.

The preservative BAK can be a source of allergic reactions. Several allergic reactions have been reported and the reference safety information has been changed accordingly.

15. RECOMMENDATION

A marketing authorisation should be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Levofloxacin 5 mg/ml eye drops are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

The efficacy of the (preserved) Oftaquix 5mg/ml Eye Drops has already been established.

SAFETY

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and some benefit has been shown to be associated with Levofloxacin 5 mg/ml eye drops. The risk benefit is therefore considered to be positive.

LEVOFLOXACIN 5MG/ML EYE DROPS

PL 16058/0009

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 24 June 2004
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 24 December 2004 and the clinical dossier on 17 May 2005
3	The applicant responded to the MHRA's requests, providing further information on the quality dossier 18 January 2005 and the clinical dossier on 9 June 2005
4	Following assessment of the application the MHRA requested further information relating to the quality dossier on 4 May 2005
5	The applicant responded to the MHRA's requests, providing further information on 12 May 2005
6	Following assessment of the response the MHRA requested further additional information relating to the quality dossier on 24 November 2005
7	The applicant responded to the MHRA's requests, providing further information on 5 January 2006
8	Following assessment of the response the MHRA requested further additional information relating to the quality dossier on 27 April 2006
9	The applicant responded to the MHRA's requests, providing further information on 16 May 2006
10	The application was determined on 21 June 2006

Product Summary for Levofloxacin 5 mg/ml eye drops (PL 16058/0009):

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin 5 mg/ml eye drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of eye drops, solution, contains 5 mg levofloxacin (as hemihydrate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, light yellow to light greenish-yellow solution, practically free of visible particulate matter.

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).

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.

While Levofloxacin 5 mg/ml eye drops have been administered for up to 15 days in a safety study, the usual treatment duration is 5 days.

The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection.

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

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, e.g. benzalkonium chloride.
(see also section 6.1.)

Levofloxacin 5 mg/ml eye drops must not be given during pregnancy and lactation.

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.

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.

This formulation of Levofloxacin 5 mg/ml eye drops contains benzalkonium chloride as a preservative and should not be used in patients continuing to wear hydrophilic (soft) contact lenses as the preservative may be absorbed and cause eye irritation.

Generally, patients should be advised not to wear any contact lenses if they have signs and symptoms of bacterial conjunctivitis.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Pregnancy and lactation

Administration of Levofloxacin 5 mg/ml eye drops during pregnancy and lactation is contra-indicated as gyrase inhibitors have been shown to cause growth disorders of weight bearing joints in animal studies. As yet, the plasma concentrations of levofloxacin reached after application to infected eyes are not known.

4.7 Effects on 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.

Common adverse reactions (1% to 10% of patients):

Ocular burning (1.6%), decreased vision (1.2%) and mucous strand (1.2%).

Uncommon adverse reactions (0.1% to 1% of patients):

Lid matting (0.9%), chemosis (0.7%), conjunctival papillary reaction (0.7%), lid oedema (0.5%), ocular discomfort (0.5%), ocular itching (0.5%), ocular pain (0.5%), conjunctival injection (0.2%), conjunctival follicles (0.2%), ocular dryness (0.2%), lid erythema (0.2%) and photophobia (0.2%).

Other reactions observed in the clinical studies included headache (0.9%) and rhinitis (0.5%). No corneal precipitates were observed in clinical studies.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinfectives. ATC code: S01AX19

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

Mode of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Break points

The following preliminary MIC breakpoints, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are suggested:

Susceptible \leq 2mg/L, resistant \geq 8mg/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.

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

Susceptible microorganisms

Aerobes, Gram-negative:

Branhamella (Moraxella) catarrhalis

Haemophilus influenzae

Neisseria gonorrhoeae

Pseudomonas aeruginosa

Aerobes, Gram-positive:

*Staphylococcus aureus**

Streptococcus pneumoniae

Streptococcus pyogenes

"Other":

Chlamydia trachomatis

* Refers only to methicillin-susceptible strains of *Staphylococcus aureus*. The majority of methicillin-resistant *Staphylococcus aureus* (MRSA) are fluoroquinolone-resistant.

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.

Cross-resistance

Cross-resistance between fluoroquinolones may occur when the mechanism of resistance is due to mutations in bacterial topoisomerases. Single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the class. Impermeability and/or drug efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physicochemical properties of the various drugs within the class and the affinity of transport systems for each drug.

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 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.

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.

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. 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 or reproduction 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 solution

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

3 years.

After first opening: to be used within 28 days.

6.4 Special precautions for storage

Keep the bottle tightly closed.

6.5 Nature and contents of container

5 ml of solution is supplied in a 5 ml white low-density polyethylene (LDPE) bottle with a LDPE dropper tip and a tan high-density polyethylene (HDPE) screw cap.

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 16058/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2006

10 DATE OF REVISION OF THE TEXT

21/06/2006

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

Levofloxacin 5 mg/ml eye drops

Levofloxacin (as hemihydrate)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Levofloxacin 5 mg/ml eye drops are and what they are used for
2. Before you use Levofloxacin 5 mg/ml eye drops
3. How to use Levofloxacin 5 mg/ml eye drops
4. Possible side effects
5. Storing Levofloxacin 5 mg/ml eye drops

The name of your medicine is **Levofloxacin 5 mg/ml eye drops**

The active substance is levofloxacin (as hemihydrate) 5 mg/ml.

Other ingredients are benzalkonium chloride solution, sodium chloride, diluted sodium hydroxide solution or diluted hydrochloric acid and Water for Injections.

Marketing Authorisation Holder and Manufacturer:

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

1. What Levofloxacin 5 mg/ml eye drops are and what they are used for

One bottle of Levofloxacin 5 mg/ml eye drops contains 5 ml solution with levofloxacin as the active ingredient.

Levofloxacin is an antibiotic of the type called fluoroquinolones (sometimes shortened to quinolones). It works by killing some types of bacteria that can cause infections.

When levofloxacin is given in eye drops, it is used in children aged 1 year or over and in adults to treat bacterial infections that affect the front surfaces of the eye. The commonest type of infection in this area is called conjunctivitis, which is an infection of the covering of the front of the eye.

Levofloxacin 5 mg/ml eye drops are not suitable for treating eye infections that have spread to the deeper layers of the eye coverings or into the fluid within the eyeball. Antibiotic tablets or injections are needed to treat these deeper and more serious infections.

2. Before you use Levofloxacin 5 mg/ml eye drops

Do not use Levofloxacin 5 mg/ml eye drops if the answer to any of the following questions is "YES". If you are not sure, ask your doctor or pharmacist first.

- Have you ever had an allergic reaction or been told that you are allergic to levofloxacin, to any other fluoroquinolone antibiotic, or to any of the other ingredients in this medicine?
- Is the person who is to have Levofloxacin 5 mg/ml eye drops less than 1 year old?
- Are you pregnant, think you may be pregnant or are you breastfeeding? Although very small amounts of levofloxacin reach the blood after inserting eye drops so that it is very unlikely that any harm could be done to the growing baby, levofloxacin can affect the growing bones and joints.

Take special care with Levofloxacin 5 mg/ml eye drops if you wear contact lenses

As with all products containing the preservative benzalkonium chloride, soft contact lenses should not be worn whilst using this medicine because this can cause irritation of the eye coverings. Generally, no types of contact lenses should be worn when the eye is infected.

Driving and using machines

If the eye drops cause blurring of your sight when you use them, you should wait until this clears before driving or operating machinery.

Using other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines - even those not prescribed. In particular, tell your doctor or pharmacist if you are applying any other type of eye drop or eye ointment before you start to use Levofloxacin 5 mg/ml eye drops.

If you are taking other eye drops, you should wait at least 15 minutes between applying Levofloxacin 5 mg/ml eye drops and any other type of eye drop.

3. How to use Levofloxacin 5 mg/ml eye drops

Always use Levofloxacin 5 mg/ml eye drops exactly as your doctor has instructed you. For patients above 1 year old, the usual dose is one to two drops in the affected eye or eyes every two hours while awake (up to a maximum of eight times per day) for the first two days and then four times daily for the next three days.

The usual total treatment course is five days, but longer courses of treatment are sometimes used. Your doctor will advise you how long to apply the drops.

If you are putting any other medicine in your eye, you should wait at least 15 minutes between applying the different types of drops.

Before applying the drops:

If possible, ask someone else to apply the drops for you. Ask them to read these instructions with you before applying the drops.

1) Wash your hands.



2) Open the bottle. **Take special care that the tip of the dropper bottle does not touch your eye, the skin around your eye or your fingers. If this happens by accident, you should tell your doctor or pharmacist so that you can obtain a clean bottle.**

Tilt your head backwards while seated, or lie down on your back.



3) Place the tip of the bottle close to your eye.



4) Pull the lower eyelid downwards and look up.



5) Press the bottle slightly and let one drop fall into the space between the lower eyelid and the eye.



6) Close your eye for a moment.

If another drop is needed, and when both eyes are to be treated, repeat steps 3 to 6.

Replace the cap securely after use.

If you forget to use the eye drops, put in the next dose as soon as you remember. Do not insert more than one or two drops to make up for the dose that you missed.

If you use more Levofloxacin 5 mg/ml eye drops than you should, flush the eye(s) with water and tell your doctor or pharmacist.

If you swallow the eye drops by accident:

The amount of levofloxacin in a bottle is too small to cause side-effects.

However, if you are concerned, tell your doctor or pharmacist who will advise you on any necessary measures.

4. Possible side-effects

Like all medicines, Levofloxacin 5 mg/ml eye drops can have side effects. About one in ten people have a side effect when using Levofloxacin 5 mg/ml eye drops. Most of these affect only the eye and may not last very long. If you have any severe or persistent side effect you should stop using Levofloxacin 5 mg/ml eye drops and seek urgent advice from your doctor.

It is possible to develop an allergic reaction to Levofloxacin 5 mg/ml eye drops even after just one dose. You notice this because your eyes may become red or itch, or the lids may be swollen. If this should happen, stop using Levofloxacin 5 mg/ml eye drops and contact your doctor immediately.

Common side effects (occurring in between one in ten and one in a hundred people) include: burning feeling in the eye, decreased vision or mucus in the eye.

Uncommon side effects (occurring in between one in a hundred and one in a thousand people) include: stinging or irritation of the eyes, eye pain, dry or sore eyes, swelling or redness (bloodshot eyes) of the conjunctivae (front covering of the eye), sensitivity to light, red, puffy or sticky eyelids, red, itchy and/or sticky eyes, headache, stuffy or runny nose.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. Storing Levofloxacin 5 mg/ml eye drops

Keep Levofloxacin 5 mg/ml eye drops out of the reach and sight of children.

Keep the bottle tightly closed.

Do not use Levofloxacin 5 mg/ml eye drops after the expiry date.

Levofloxacin 5 mg/ml eye drops are to be used within 28 days after first opening the bottle. Any remaining solution should be returned to your pharmacist for safe disposal.

This leaflet was approved on May 2005.

LABELLING

PL 16058/0009

Carton 5 ml dose:



PL 16058/0009

Label of 5 ml container

100% size



200% size

