SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[MOXIFLOXACIN] 5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.
Each eye drop contains 190 micrograms of moxifloxacin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops solution

Clear, greenish-yellow solution.
The osmolality of the product is 290 mOsmol/Kg ± 5% and pH is between.6.3 and 7.3.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of purulent bacterial conjunctivitis, caused by moxifloxacin susceptible strains (see sections 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
For ocular use only. Not for injection. [Moxifloxacin Eye Drops, Solution] should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

Use in adults including the elderly
The dose is one drop in the affected eye(s) 3 times a day.
The infection normally improves within 5 days and treatment should then be continued for a further 2-3 days. If no improvement is observed within 5 days of initiating therapy, the diagnosis and/or treatment should be reconsidered. The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection.

Paediatric population
No dosage adjustment is necessary.

Use in hepatic and renal impairment
No dosage adjustment is necessary.

Method of administration

Ocular use

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.
In order to prevent the drops from being absorbed via the nasal mucosa, particularly in new-born

infants or children, the nasolacrimal ducts should be held closed for 2 to 3 minutes with the fingers after administering the drops.
If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching.

If an allergic reaction to [MOXIFLOXACIN] occurs, discontinue use of the medicinal product. Serious acute hypersensitivity reactions to moxifloxacin or any other product ingredient may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated.

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.

Data are very limited to establish efficacy and safety of [MOXIFLOXACIN] in the treatment of conjunctivitis in neonates. Therefore use of this medicinal product to treat conjunctivitis in neonates is not recommended.

[MOXIFLOXACIN] should not be used for the prophylaxis or empiric treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum, because of the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae*. Patients with eye infections caused by *Neisseria gonorrhoeae* should receive appropriate systemic treatment.

The medicinal product is not recommended for the treatment of *Chlamydia trachomatis* in patients less than 2 years of age as it has not been evaluated in such patients. Patients older than 2 years of age with eye infections caused by *Chlamydia trachomitis* should receive appropriate systemic treatment.

Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomitis* or *Neisseria gonorrhoeae*.

Patients should be advised not to wear contact lenses if they have signs and symptoms of a bacterial ocular infection.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with [MOXIFLOXACIN] 5 mg/ml Eye Drops, Solution. Given the low systemic concentration of moxifloxacin following topical ocular administration of the medicinal product (see Section 5.2), drug interactions are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of [MOXIFLOXACIN] in pregnant women. However, no

effects on pregnancy are anticipated since the systemic exposure to moxifloxacin is negligible. The medicinal product can be used during pregnancy

Breast-feeding
It is unknown whether moxifloxacin is excreted in human breast milk. Animal studies have shown excretion of low levels in breast milk after oral administration of moxifloxacin. However, at therapeutic doses of [MOXIFLOXACIN] no effects on the suckling child are anticipated. The medicinal product can be used during breast-feeding.

4.7 Effects on the ability to drive and use machines

As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 1,740 patients, [MOXIFLOXACIN] was administered up to 8 times a day, with 1,452 of these patients receiving treatment 3 times daily. The overall safety population that received the medicinal product consisted of 877 patients from the United States and Canada, 586 patients from Japan and 277 patients from India. No serious ophthalmic or systemic undesirable effects related to the medicinal product were reported in any of the clinical studies. The most frequently reported treatment-related undesirable effects with the medicinal product were eye irritation and eye pain, occurring at an overall incidence of 1 to 2%. These reactions were mild in 97% of those patients who experienced them, with only 1 patient discontinuing therapy as a result.

Tabulated summary of adverse reactions

The following undesirable effects were assessed to be treatment-related and are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), or very rare (<1/10,000) or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

<u>Blood and lymphatic system disorders</u>
Uncommon: haemoglobin decreased

<u>Nervous system disorders</u>
Common: dysgeusia
Uncommon: headache, paraesthesia

<u>Eye disorders</u>
Common: eye pain, eye irritation, dry eye, eye pruritus, conjunctival hyperaemia, ocular hyperaemia

Uncommon: corneal epithelium defect, punctate keratitis, corneal staining, conjunctival haemorrhage, conjunctivitis, eye swelling, ocular discomfort, vision blurred, visual acuity reduced, eyelid disorder, erythaema of eyelid, abnormal sensation in eye

<u>Respiratory, thoracic, and mediastinal disorders</u>
Uncommon: nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)

<u>Gastrointestinal disorders</u>
Uncommon: vomiting

Hepatobiliary disorders
Uncommon: alanine aminotransferase increased, gamma-glutamyltransferase increased

Adverse reactions identified from post-marketing experience that have not been reported previously in clinical trials with the medicinal product include the following. The frequency category in which these adverse reactions occur is not known and cannot be estimated from the available data.

Cardiac disorders:
Not known: palpitations

Nervous system disorders:
Not known: dizziness

Eye disorders:
Not known: endophthalmitis, ulcerative keratitis, corneal erosion, corneal abrasion, intraocular pressure increased, corneal opacity, corneal infiltrates, corneal deposits, eye allergy, keratitis, corneal oedema, photophobia, corneal disorder, blepharitis, eyelid oedema, lacrimation increased, eye discharge, foreign body sensation in eyes

Respiratory, thoracic, and mediastinal disorders:
Not known: dyspneoa

Gastrointestinal disorders:
Not known: nausea

Skin and subcutaneous tissue disorders:
Not known: erythema, rash, pruritus

Immune system disorders:
Not known: hypersensitivity

Paediatric population
Based on data from clinical trials involving paediatric patients, including neonates (see section 5.1), the type and severity of adverse reactions in the paediatric population are similar to those 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

No case of overdose with [MOXIFLOXACIN] has been reported. The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of the medicinal product.

The total amount of moxifloxacin in a single container is too small to induce adverse effects after accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives, other anti-infectives, ATC code: S01A X22

Mechanism of action Moxifloxacin, a fourth-generation fluoroquinolone, inhibits the DNA gyrase and topoisomerase IV required for bacterial DNA replication, repair, and recombination.

Mechanisms of Resistance:
Resistance to fluoroquinolones, including moxifloxacin, occurs generally by chromosomal mutations in genes encoding DNA gyrase and topoisomerase IV. In Gram-negative bacteria, moxifloxacin resistance can be due to mutations in *mar* (multiple antibiotic resistance) and the *qnr* (quinolone resistance) gene systems. Cross-resistance with beta-lactams, macrolides and aminoglycosides is not expected due to differences in mode of action.

Breakpoints

• The minimal inhibitory concentration (MIC) breakpoints (mg/l) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:
• *Staphylococcus* species $S \leq 0.5$, $R > 1$
• *Streptococcus A,B,C,G* $S \leq 0.5$, $R > 1$
• *Streptococcus pneumoniae* $S \leq 0.5$, $R > 0.5$
• *Haemophilus influenzae* $S \leq 0.5$, $R > 0.5$
• *Moraxella catarrhalis* $S \leq 0.5$, $R > 0.5$
• Enterobacteriaceae $S \leq 0.5$, $R > 1$
• Not species-related $S \leq 0.5$, $R > 1$

The *in vitro* breakpoints have been useful in predicting clinical efficacy of moxifloxacin when administered systemically. These breakpoints might not be applicable on topical ocular use of the medicinal product as higher concentrations are obtained in the eye and the local physical/chemical circumstances can influence the activity of the product on the site of administration.

Susceptibility:
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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of moxifloxacin in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms:
Corynebacterium species including
Corynebacterium diphtheriae
Staphylococcus aureus (methicillin susceptible)
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus viridans Group
Aerobic Gram-negative micro-organisms*:*
Enterobacter cloacae
Haemophilus influenzae
Klebsiella oxytoca
Moraxella catarrhalis
Serratia marcescens
Anaerobic micro-organisms:
Proprionibacterium acnes
Other micro-organisms:
Chlamydia trachomatis

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms: *Staphylococcus aureus* (methicillin resistant) *Staphylococcus,* coagulase-negative species (methicillin resistant) **Aerobic Gram-negative micro-organisms*:*** *Neisseria gonorrhoeae* **Other micro-organisms:** None

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-negative micro-organisms*:* *Pseudomonas aeruginosa* **Other micro-organisms:** None

5.2 Pharmacokinetic properties

Following topical ocular administration of [MOXIFLOXACIN], moxifloxacin was absorbed into the systemic circulation. Plasma concentrations of moxifloxacin were measured in 21 male and female subjects who received bilateral topical ocular doses of the medicinal product 3 times a day for 4 days. The mean steady-state C_{max} and AUC were 2.7 ng/ml and 41.9 ng·hr/ml, respectively. These exposure values are approximately 1,600 and 1,200 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure following administration to the eye indicating little relevance to clinical use.

As with other quinolones, moxifloxacin was also genotoxic *in vitro* in bacteria and mammalian cells. As these effects can be traced to the interaction with bacterial gyrase and in considerably higher concentrations to the interaction with topoisomerase II in mammalian cells, a threshold level for genotoxicity can be assumed. In *in vivo* tests, no evidence of genotoxicity was found, despite high doses of moxifloxacin. The therapeutic doses for human use therefore provide adequate safety margin. No indication of a carcinogenic effect was observed in an initiation promotion model in rats.

Unlike other quinolones, moxifloxacin showed no phototoxic or photogenotoxic properties in extensive *in vitro* and *in vivo* studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Boric acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Discard 4 weeks after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

Transparent-sterilized 10ml LDPE bottle with LDPE dropper tip and HDPE tamper-proof screw-cap, consisting of a natural, low density polyethylene ophthalmic dispenser with a sealed dropper tip and a two-piece white –high density polyethylene closure cap assembly, containing 5ml of the ophthalmic solution.

Pack size: box containing 1 bottle

6.6 Special precautions for disposal and other handling

Any unused 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
<To be completed nationally>

10. DATE OF REVISION OF THE TEXT
<To be completed nationally>