MOXICIP KT Eye Drops (Moxifloxacin 0.5% + Ketorolac tromethamine 0.5%)

Composition

Each ml contains:
Moxifloxacin Hydrochloride Ph.Eur
Equivalent to Moxifloxacin .......... 0.5% w/v
Ketorolac Tromethamine USP ..........0.5% w/v
Isotonic Aqueous Vehicle ..................q.s

Dosage Form

Ophthalmic Solution (Preservative free)

Description

MOXICIP KT ophthalmic solution is a topical sterile multidose combination of nonsteroidal anti-inflammatory drug (NSAID) and antibiotic for ophthalmic use.

MOXICIP KT ophthalmic solution contains moxifloxacin hydrochloride 0.5% w/v and ketorolac tromethamine 0.5% w/v.

Moxifloxacin is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

Ketorolac is a member of the pyrrolopyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDS).

Pharmacology

Pharmacodynamics

Moxifloxacin
Moxifloxacin is an 8-methoxy fluoroquinolone with a diazabicyclononyl ring at the C7 position. The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial-cell division.
The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, aminoglycosides, or tetracyclines. Therefore, moxifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to moxifloxacin. There is no cross-resistance between moxifloxacin and the aforementioned classes of antibiotics. Cross resistance has been observed between systemic moxifloxacin and some other quinolones.

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 \textit{mar} (multiple antibiotic resistance) and the \textit{qnr} (quinolone resistance) gene systems. Cross-resistance with beta-lactams, macrolides and aminoglycosides is not expected due to differences in mode of action.

\textit{In vitro} resistance to moxifloxacin develops via multiple-step mutations. Resistance to moxifloxacin occurs \textit{in vitro} at a general frequency of between $1.8 \times 10^{-9}$ to $<1 \times 10^{-11}$ for Gram-positive bacteria.

Breakpoints
The minimal inhibitory concentration (MIC) breakpoints (mg/l) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>MIC Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Staphylococcus species}</td>
<td>S ≤ 0.5, R &gt; 1</td>
</tr>
<tr>
<td>\textit{Streptococcus A,B,C,G}</td>
<td>S ≤ 0.5, R &gt; 1</td>
</tr>
<tr>
<td>\textit{Streptococcus pneumoniae}</td>
<td>S ≤ 0.5, R &gt; 0.5</td>
</tr>
<tr>
<td>\textit{Haemophilus influenzae}</td>
<td>S ≤ 0.5, R &gt; 0.5</td>
</tr>
<tr>
<td>\textit{Moraxella catarrhalis}</td>
<td>S ≤ 0.5, R &gt; 0.5</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>S ≤ 0.5, R &gt; 1</td>
</tr>
<tr>
<td>Not species-related</td>
<td>S ≤ 0.5, R &gt; 1</td>
</tr>
</tbody>
</table>

The \textit{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.

Moxifloxacin has been shown to be active against most strains of the following microorganisms:

Aerobic Gram-positive Microorganisms
Corynebacterium species\(^1\) including
- *Corynebacterium diphtheriae*
- *Micrococcus luteus*\(^1\)
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Staphylococcus haemolyticus*
- *Staphylococcus hominis*
- *Staphylococcus warneri*\(^1\)
- *Streptococcus pneumoniae*
- *Streptococcus viridans* group

Aerobic Gram-negative Microorganisms
- *Acinetobacter lwoffii*\(^1\)
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*\(^1\)

Other Microorganisms
- *Chlamydia trachomatis*

\(^1\)Efficacy for this organism was studied in fewer than 10 infections.

Species for which Acquired Resistance may be a Problem

**Aerobic Gram-positive Microorganisms**
- *Staphylococcus aureus* (methicillin resistant)
- *Staphylococcus*, coagulase-negative species (methicillin resistant)

**Aerobic Gram-negative Microorganisms**
- *Neisseria gonorrhoeae*

**Other Microorganisms**
- None

Inherently Resistant Organisms

**Aerobic Gram-negative Microorganisms**
- *Pseudomonas aeruginosa*

**Other Microorganisms**
- None

The following *in vitro* data are also available, but their clinical significance in opthalmic infections is unknown. The safety and effectiveness of moxifloxacin in treating opthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and opthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2μg/ml or less (systemic susceptible breakpoint) against most (≥ 90%)
strains of the following ocular pathogens.

Aerobic Gram-positive Microorganisms
Listeria monocytogenes
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus mitis
Streptococcus pyogenes
Streptococcus Group C, G and F

Aerobic Gram-negative Microorganisms
Acinetobacter baumannii
Acinetobacter calcoaceticus
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Pseudomonas stutzeri

Anaerobic Microorganisms
Clostridium perfringens
Fusobacterium species
Prevotella species
Propionibacterium acnes

Other Microorganisms
Chlamydia pneumoniae
Legionella pneumophila
Mycobacterium avium
Mycobacterium marinum
Mycoplasma pneumoniae

Ketorolac Tromethamine
Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and antipyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Prostaglandins have been shown in many animal models to be mediators
of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure. Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. Ocular administration of ketorolac tromethamine reduces prostaglandin E2 (PGE2) levels in aqueous humor.

Results from clinical studies indicate that ketorolac tromethamine has no significant effect on intraocular pressure.

### Pharmacokinetics

**Moxifloxacin**

Plasma concentrations of moxifloxacin were measured in healthy adult male and female subjects who received bilateral topical ocular doses of Moxifloxacin 3 times a day. The mean steady-state $C_{\text{max}}$ (2.7 ng/mL) and estimated daily exposure AUC (45 ng hr/mL) values were 1,600 and 1,000 times lower than the mean $C_{\text{max}}$ and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

**Ketorolac Tromethamine**

Two drops of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved a mean ketorolac concentration of 95 ng/mL in the aqueous humor of 8 of 9 eyes tested (range 40 to 170 ng/mL).

One drop of 0.5% ketorolac tromethamine ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye TID in 26 healthy subjects. Five (5) of 26 subjects had detectable concentrations of ketorolac in their plasma (range 11 to 23 ng/mL) at Day 10 during topical ocular treatment. The range of concentrations following TID dosing of 0.5% ketorolac tromethamine ophthalmic solution are approximately 4 to 8% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg ketorolac in humans (290 ± 70 ng/mL).

### Indications

NSAID responsive inflammatory ocular conditions for which a NSAID is indicated and where superficial bacterial ocular infection or the risk of bacterial ocular infection exists and where the inherent risk of NSAID use in certain infective conjunctivitides is accepted to obtain a diminution in oedema and inflammation.

Topical NSAID like ketorolac tromethamine is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

### Dosage And Administration
Instil one drop in the affected eye 3 times a day or as directed by the physician.

**Contraindications**

Moxifloxacin and ketorolac ophthalmic solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, ketorolac or to any of the components in this medication.

The potential exists for cross-sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs. Ketorolac is contraindicated in individuals who have previously exhibited sensitivities to these drugs.

**Warnings And Precautions**

**General**

Moxifloxacin

NOT FOR INJECTION.

Moxifloxacin ophthalmic solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemically administered quinolones, including moxifloxacin, 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, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as 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. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

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 gonococcalophthalmia 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 trachomatis* 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 trachomatis* or *Neisseria gonorrhoeae*.

Ketorolac Tromethamine

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing.

Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. There have been reports of bronchospasm or exacerbation of asthma in patients with the use of ketorolac tromethamine ophthalmic solution in patients who have either a known hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs or a past medical history of asthma. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

In common with other anti-inflammatory drugs, ketorolac may mask the usual signs of infection.

With some NSAIDs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that ketorolac ophthalmic solution should be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

Concomitant use of ketorolac and topical corticosteroids should be exercised with caution in patients susceptible to corneal epithelial breakdown.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Post marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post marketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

**Effect on 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.
Drug interactions

Moxifloxacin
Drug-drug interaction studies have not been conducted with moxifloxacin. In vitro studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by this cytochrome P450 isozymes.

Ketorolac Tromethamine
No interaction studies have been performed.
Ketorolac has been safely administered with systemic and ophthalmic medications such as antibiotics, sedatives, beta blockers, carbonic anhydrase inhibitors, miotics, mydriatics, local anaesthetics and cycloplegics.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Hence, MOXICIP KT ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation
Caution should be exercised when MOXICIP KT ophthalmic solution is administered to a nursing mother.

Paediatric Use
Safety and efficacy in paediatric patients below the age of 3 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Undesirable Effects
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Moxifloxacin
The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

Non-ocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

In clinical studies involving 1,740 patients, moxifloxacin ophthalmic solution 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.

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.

Blood and Lymphatic System Disorders
Uncommon: haemoglobin decreased

Nervous System Disorders
Common: dysgeusia
Uncommon: headache, paraesthesia

Eye Disorders
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, erythema of eyelid, abnormal sensation in eye

Respiratory, Thoracic, and Mediastinal Disorders
Uncommon: nasal discomfort, pharyngolaryngeal pain, sensation of foreign body (throat)

Gastrointestinal Disorders
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 moxifloxacin 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: dyspnoea

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, the type and severity of adverse reactions in the paediatric population are similar to those in adults

Ketorolac Tromethamine
The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solution have been transient stinging and burning on instillation. These events were reported by up to 40% of patients participating in clinical trials.

Other adverse events occurring approximately 1% to 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal oedema, iritis, ocular inflammation, ocular irritation, superficial keratitis and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine include: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

The following adverse reactions have been identified during post-marketing use of ketorolac tromethamine ophthalmic solution 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine 0.5%, or a combination of these factors, include bronchospasm or exacerbation of asthma, corneal erosion, corneal perforation, corneal thinning and epithelial breakdown.

The frequency of adverse reactions documented during clinical trials is given below and is defined as follows: Very
Common $\geq 1/10$; Common ($1/100 \text{ to } <1/10$); Uncommon ($1/1,000 \text{ to } <1/100$); Rare ($1/10,000 \text{ to } <1/1,000$); Very Rare ($<1/10,000$); Not Known (cannot be estimated from available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Immune System disorders
Common: Hypersensitivity including localised allergic reactions

Nervous System Disorders
Uncommon: Headache

Eye Disorders
Very common: Eye irritation (including burning sensation), Eye pain (including stinging)
Common: Superficial (punctate) keratitis, eye and/or eyelid oedema, ocular pruritus, conjunctival hyperaemia, eye infection, eye inflammation
Uncommon: Corneal ulcer, corneal infiltrates, eye dryness, blurred and/or diminished vision, epiphora, iritis
Not known: Corneal damage, e.g. thinning, erosion, epithelial breakdown and perforation

Respiratory, Thoracic and Mediastinal Disorders
Not known: Bronchospasm or exacerbation of asthma

None of the typical adverse reactions reported with the systemic non-steroidal anti-inflammatory agents (including ketorolac) have been observed at the doses used in topical ophthalmic therapy.

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**Overdosage**

Data not available

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**Incompatibility**

Not applicable

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**Shelf-Life**

24 months

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**Packaging Information**

MOXICIP KT: Vial of 5ml
MOXICIP KT ophthalmic solution should not be administered while wearing contact lenses. Avoid contaminating the applicator tip with material from the eye, fingers or other source. Systemically administered quinolones including moxifloxacin have been associated with hypersensitivity reactions, even following a single dose.

Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Last updated: December 2013
Last reviewed: December 2013

MOXICIP KT Eye Drops

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