- Broad-spectrum antibacterial ophthalmic solution -

**OZEX® ophthalmic solution 0.3%**

*< Tosufloxacin tosilate ophthalmic solution>*

Designated drug and Prescription drug

**CONTRAINDICATIONS (OZEX® ophthalmic solution is contraindicated in the following patients.)**

Patients with a history of hypersensitivity to any of the ingredients of this product or to quinolone antimicrobial agents.

**DESCRIPTION**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>OZEX® ophthalmic solution 0.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Tosufloxacin tosilate</td>
</tr>
<tr>
<td>Content (per 1mL)</td>
<td>3 mg (2.04 mg of tosufloxacin)</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Aluminum potassium sulfate hydrate, sodium borate, sodium chloride, pH adjuster</td>
</tr>
<tr>
<td>Color/Dosage form</td>
<td>Colorless, clear, sterile aqueous ophthalmic solution</td>
</tr>
<tr>
<td>pH</td>
<td>4.9-5.5</td>
</tr>
<tr>
<td>Osmotic pressure ratio</td>
<td>0.9-1.1 (vs. physiological saline)</td>
</tr>
</tbody>
</table>

**INDICATIONS**

*<Indicated bacteria>*


*<Indications>*

Blepharitis, dacryocystitis, hordeolum, conjunctivitis, tarsadeatitis, keratitis (including corneal ulcer), sterilization therapy during ophthalmic surgery

**CONTRAINDICATIONS**

Efficacy of post-operative administration in sterilization therapy during ophthalmic surgery has not been established. (See Clinical Studies, Section 3, "Efficacy in Sterilization Therapy during Ophthalmic Surgery").

**DOSAGE AND ADMINISTRATION**

The usual adult and child dosage is one drop per administration three times per day. The dosage may be adjusted according to the disease and the patient's condition.

*<Precautions>*

1. As a general rule, the duration of administration of this drug should be limited to the minimum period required for the treatment of the patient's condition, after susceptibility of the microorganism to the drug has been confirmed, in order to prevent the emergence of drug-resistant microorganisms.

2. Since therapeutic effects may be observed in children in a shorter period of time than in adults, children should be monitored carefully and caution should be used to prevent unnecessary use.

3. The safety of increased dosages in children has not been confirmed.

**PRECAUTIONS**

1. **Adverse Reactions**

Sixteen incidents of adverse reactions to the drug were reported in 15 adults (2.42%) of a total of 620 patients (539 adults, 81 children (including 62 infants and 11 newborns)) in clinical studies until the time of approval. The major adverse reactions were 6 incidences of eye irritation (0.97%), and 4 incidents of corneal disorders such as punctate keratitis (0.65%).

1. **Clinically significant adverse reactions (Similar drugs)**

Shock and anaphylactoid reactions: Since shock and anaphylactoid reactions have been reported with other ophthalmic new quinolone antimicrobial agents,
patients should be carefully monitored. If symptoms such as erythema, rash, dyspnoea, decreased blood pressure or blepharoeedema are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

(2) Other adverse reactions
If the following adverse reactions are observed, appropriate therapeutic measures such as discontinuation of the administration of this drug, should be taken according to the patient’s condition.

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Ocular disorder</th>
<th>Sensation of foreign body, corneal deposits, conjunctivitis (conjunctival hyperemia, edema, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye irritation</td>
<td>1%&gt; 0.5%</td>
<td>Ophtalmalgia, punctate keratitis</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0.5%&gt; 0.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Precautions concerning Use
(1) The drug should only be used for ophthalmic use.
(2) Patients must be instructed not to allow the tip of the container to come in direct contact with the eye during use to prevent contamination.
(3) Concomitant use with ophthalmic solutions for which changes have been observed should be avoided as a general rule (See "Precautions for Handling").

3. Other Precautions
It has been reported that the active ingredient of this drug was attached to the soft contact lens and that the lens became clouded.

PHARMACOKINETICS

1. Blood concentration and conjunctival sac concentration
The serum tosufloxacin concentration 1.5 hours after the final instillation when the drug was administered to the eyes of healthy adults at one drop per administration three times per day for 14 days was below the quantification limit (<0.0347 μg/mL). In addition, the serum tosufloxacin concentration 24 hours after the first instillation on the 14th day of instillation when the drug was administered to the eyes of healthy adults at one drop per administration eight times per day for 14 days, was also below the quantification limit (<0.0347 μg/mL), and the concentration in the conjunctival sac was 2.0 μg/mL.

2. Transfer to eye tissue in animals (reference: rabbits, dogs)
(1) Conjunctival sac concentration
The concentration of tosufloxacin in the conjunctival sac of colored rabbits following instillation of the drug at 40 μL per administration was 168 μg/mL at 5 minutes, 3.31 μg/mL at 4 hours, and 0.670 μg/mL at 6 hours after instillation.

(2) Eye tissue concentration
1) 14C-labeled tosufloxacin tosilate ophthalmic solution 0.3% was widely distributed throughout all eye tissue, excluding the vitreous body, at 1 hour after instillation when administered at 40 μL per administration to colored rabbits, and radioactive concentrations were 436 ng eq./g in the palprebral conjunctiva, 128 ng eq./g in the bulbar conjunctiva, 89.3 ng eq./g in the anterior aqueous humor, and 1800 ng eq./g in the cornea. In addition, the radioactive concentrations in melanin-containing tissue consisting of the iris/ciliary body and choroida/retina were 421 ng eq./g and 249 ng eq./g, respectively, 1 hour after instillation, and 3250 ng eq./g and 759 ng eq./g, respectively, 24 hours after instillation.
2) When 14C-labeled tosufloxacin tosilate was repetitively orally administered to beagle dogs at a dose of 20 mg/kg once a day for 14 days, the radioactive concentrations in the choroida/pigment epithelium and iris/ciliary body were 322 μg eq./g and 425 μg eq./g, respectively, 12 hours after completion of administration, and gradually decreased until they were no longer detected 360 days after completion of administration.
3) In a toxicity study consisting of 13-week repetitive instillation using juvenile rabbits, the mean concentrations of tosufloxacin in the palprebral conjunctiva, cornea, choroida/pigment epithelium and iris/ciliary body in a tosufloxacin dose group were somewhat higher (1.4 to 2.3 times) than in the case of 39-week repetitive instillation of tosufloxacin to mature rabbits. On the other hand, drug concentrations in the bulbar conjunctiva and anterior aqueous humor exhibited nearly equal values in juvenile and mature rabbits.

CLINICAL STUDIES

1. Clinical efficacy by disease
Clinical efficacy against various diseases in phase III clinical studies and open clinical studies of the drug conducted on 304 patients with external eye infections was as indicated in the table below.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Efficacy (effective or better)</th>
<th>Overall clinical studies (including clinical study in children)</th>
<th>Clinical study in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharitis</td>
<td>90.0% (9/10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dacryocystitis</td>
<td>93.8% (15/16)</td>
<td>100% (3/5)</td>
<td></td>
</tr>
<tr>
<td>Hordeolum</td>
<td>97.8% (45/46)</td>
<td>100% (6/6)</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>94.4% (187/198)</td>
<td>97.6% (40/41)</td>
<td></td>
</tr>
<tr>
<td>Tarsadenitis</td>
<td>87.0% (20/23)</td>
<td>100% (1/1)</td>
<td></td>
</tr>
<tr>
<td>Keratitis (including corneal ulcer)</td>
<td>100% (11/11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1: Including 4 cases of corneal ulcer
2. Clinical efficacy by indicated bacteria

Clinical efficacy by indicated bacteria isolated from the patients indicated above was as indicated in the table below.

<table>
<thead>
<tr>
<th>Indicated bacteria</th>
<th>Efficacy % (effective or better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>94.1% (128/136)</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>100% (16/16)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>100% (10/10)</td>
</tr>
<tr>
<td>Moraxella spp. (Moraxella(Branhemella) catarrhalis)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
<td>98.7% (77/78)</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>100% (1/1)</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>100% (35/35)</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td>Stenotrophomonas(Xanthomonas) maltophilia</td>
<td>66.7% (2/3)</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>86.8% (79/91)</td>
</tr>
</tbody>
</table>

*2: each species counted as one case when multiple species were detected.

3. Efficacy in sterilization therapy during ophthalmic surgery

Antibacterial efficacy in preoperative sterilization performed on patients scheduled for ophthalmic surgery was observed in 47 cases where sterilization was achieved among 64 evaluated cases (sterilization rate: 73.4%). Furthermore, the drug was instilled at one drop per administration, 5 times per day for 2 days.

PHARMACOLOGY

1. Antibacterial activity

Tosufloxacin, the active form of the drug, possesses a broad antibacterial spectrum and demonstrates potent antibacterial activity in vitro against various causative organisms of eye infections, including Gram-positive organisms such as Staphylococcus spp., Streptococcus spp., Streptococcus pneumoniae, Enterococcus spp., Micrococcus spp. and Corynebacterium spp., Gram-negative organisms such as Moraxella spp., Klebsiella spp., Enterobacter spp., Proteus spp., Morganella morganii, Providencia spp., Haemophilus influenzae, Haemophilus aegyptius (Koch-Weeks bacillus), Pseudomonas spp., Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas (Xanthomonas) maltophilia, Acinetobacter spp., and anaerobic organisms such as Propionibacterium acnes.

2. Mechanism of action

The drug acts bactericidally by acting on DNA gyrase and topoisomerase IV, which convert the higher structure of bacterial DNA, to inhibit DNA replication.

3. Therapeutic effect in experimental infections

The drug had a therapeutic effect in an experimental eye infection model prepared by inoculating clinically isolated strains of P. aeruginosa or S. epidermidis into rabbit corneal parenchyma.

PHYSICOCHEMISTRY

Nonproprietary name: Tosufloxacin tosilate hydrate (JAN), Tosufloxacin (INN)

Chemical name: (±)-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid p-toluenesulfonate hydrate

Abbreviation: TFLX

Molecular formula: C_{19}H_{15}F_{3}N_{4}O_{3}

Abbreviation: TFLX

Molecular weight: 594.56

Structural formula:

```
H2N  F
N = N   N
F

\( \text{CH}_3 \text{SO}_3 \text{H} \cdot \text{H}_2\text{O} \)
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Description: Tosufloxacin tosilate occurs as a pale yellowish white crystalline powder. It is freely soluble in N,N-dimethylformamide, sparingly soluble in methanol, and practically insoluble in water and ethanol (95). Methanol solution (1->100) does not have rotatory power. Melting point: 254°C (decomposition)

PRECAUTIONS FOR HANDLING

Changes when mixed with other ophthalmic solutions

1 mL of the drug and 1 mL of mixed drug are placed in a glass tube and mixed for 10 seconds with a mixer followed by observation of changes in appearance.

- Drugs causing changes when mixed
  - Rinderon solution, Niflan ophthalmic solution, Diclod ophthalmic solution, Bronuck ophthalmic solution, Rinderon A ophthalmic and nasal solution, Ecobil ophthalmic solution, Rizaben eye drops, Intal eye drops, Tathom ophthalmic solution, Mydrin-M ophthalmic solution, Xalatan eye drops, Timoptol ophthalmic solution 0.25%, Timoptol YE ophthalmic solution 0.5%, Trusopt ophthalmic solution 1%, Rysmon TG ophthalmic solution 2%, Flaviton eye drops

- Drugs not causing changes when mixed
  - Tobracin eye drops, Santemycin ophthalmic solution, Zaditen ophthalmic solution, Mydriant eye drops, Santemycin ophthalmic solution, Zaditen ophthalmic solution, Mydriant-P ophthalmic solution, Rescula eye drops, Sancoba ophthalmic solution

*3: Change of appearance (white turbidity) was observed immediately after mixing or after allowing to stand for one hour at room temperature. It was estimated that the white turbidity would be due to the deposition of the active ingredient, being caused by disturbing of the chelate
equilibrium of tosufloxacin and aluminum ion, which was the dissolution mechanism of the product, with edetic acid, citric acid or phosphoric acid, in other ophthalmic solutions.

PACKAGING
OZEX® ophthalmic solution 0.3%:
5 mL x 5 plastic bottles, 5 mL x 10 plastic bottles

REFERENCES
1) Nidek Co., Ltd., internal document
2) Nidek Co., Ltd., internal document
10) Toyama Chemical Co., Ltd., internal document.
12) Toyama Chemical Co., Ltd., internal document
15) Toyama Chemical Co., Ltd., internal document
16) Toyama Chemical Co., Ltd., internal document

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