Tarivid® Ophthalmic Ointment
(Ofloxacin 0.3%)

1. Name of the Medical Product

1.1. Product name

Tarivid Ophthalmic Ointment

1.2. Strength

Ofloxacin 0.3%

1.3. Pharmaceutical dosage form

Ophthalmic ointment

2. Quality and Quantitative Composition

Each gram of ointment contains 3.0 mg of ofloxacin.

3. Pharmaceutical Form

This product is a light yellow ophthalmic ointment.

4. Clinical Particulars

4.1. Therapeutic indications

For treatment of blepharitis, dacryocystitis, hordeolum, conjunctivitis, tarsadenitis, keratitis (including corneal ulcer), aseptic treatment during a perioperative period for ocular surgery.

4.2. Posology and method of administration

Usually, the small amount of ointment is to be applied to the affected eye 3 times a day. The treatment with this drug should be limited to the minimum period required for the eradication of the infection. The dosage may be adjusted according to the patient's symptoms.

4.3. Contraindications

Patients with a history of hypersensitivity to the ingredient of this product or any quinolone antibiotics.

4.4. Special warning and precautions for use

4.4.1 Precautions concerning use

1) In order to avoid the emergence of resistant bacteria, bacterial susceptibility should be confirmed and treatment with this drug should be limited to the minimum period required for the eradication of the infection.
2) Avoid long-term use. The duration of treatment of conjunctivitis by *Chlamydia trachomatis* with this drug should be 8 weeks as a standard. The continued administration thereafter should be made with caution.

3) Route of administration: ophthalmic use only.

4.5. Interaction with other medical products and other forms of interactions

Not particularly specified

4.6. Pregnancy and lactation

The safety of this product during pregnancy has not been established

There are no adequate data for the use of this product in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

It is unknown whether ofloxacin are excreted in human milk.

Therefore, this product should not be used in pregnant women or women who may possibly be pregnant and breastfeeding woman unless the expected therapeutic benefits are judged to outweigh the possible risks associated with treatment.

4.7. Effects on ability to drive and use machine

As with any ocular treatment, if transient blurred vision occurs when apply the product, patients should be advised not to drive or use machines until their vision has cleared.

4.8. Undesirable effects

Adverse reactions were reported in 14 of 2,360 patients (0.59%) in clinical trials and post marketing surveillance in Japan. The major adverse reactions were eyelid itching in 3 patients (0.13%), swelling of eyelid in 3 patients (0.13%), blepharitis in 2 patients (0.08%), conjunctival hyperaemia in 2 patients (0.08%), eye pain in 2 patients (0.08%), and redness of eyelid in 2 patients (0.08%), etc.. [At the end of the re-examination period]

1) Clinically significant adverse reactions

Shock, anaphylaxis (incidence unknown): Since shock and anaphylaxis may occur, patients should be carefully observed. If any symptoms such as erythema, rash, dyspnoea, decreased blood pressure, and eyelid oedema, etc. are observed, administration should be discontinued and appropriate measures should be taken.

2) Other adverse reactions

If any adverse reactions are observed, appropriate measures such as discontinuing administration should be taken.

Incidence / Type	Incidence unknown	5% > ≥0.1%	<0.1%
Hypersensitivity	Rash, urticaria	Itching	Blepharitis (redness of eyelid and eyelid oedema, etc.), dermatitis eyelid

Ophthalmic	Conjunctivitis (conjunctival hyperaemia and conjunctival oedema, etc.), corneal disorder including keratitis superficial diffuse, etc.	–	–

4.9. Overdose

Not particularly specified

5. Pharmacological Properties

5.1. Pharmacodynamic properties

1) Mechanism of action

Ofloxacin is considered to inhibit DNA synthesis of bacteria specifically by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV activities. Its effect is bactericidal, and bacteriolysis is observed at the MICs. Ofloxacin has also been recognized to destroy the elementary body of *Chlamydia trachomatis* in its growth cycle.

2) Antibacterial activity

Ofloxacin exerts a broad-spectrum potent antibacterial activity against organisms causing ophthalmological infections, including gram-positive bacteria (*Staphylococcus* sp., *Streptococcus* sp. [including *S. pneumoniae*], *Micrococcus* sp., *Corynebacterium* sp., etc.), gram-negative bacteria (*Pseudomonas* sp. [including *P. aeruginosa*], *Haemophilus* sp., *Moraxella* sp., *Serratia* sp., *Klebsiella* sp., *Proteus* sp. *Acinetobacter* sp., etc.), and Anaerobic bacteria (*Propionibacterium acnes*, etc.). Ofloxacin is also active against *Chlamydia* species, including *Chlamydia trachomatis*. It is recognized that *Chlamydia* species hardly acquire resistance to ofloxacin.

3) Clinical Efficacy

Clinical studies conducted in 126 patients with external ocular infections showed the efficacy of this drug as below.

Clinical efficacy classified by diseases (internally collected upon approval)

Disease	Efficacy rate* (%)
Blepharitis	100.0 (6/6)
Dacryocystitis	85.7 (6/7)
Hordeolum	87.5 (7/8)
Conjunctivitis**	96.0 (48/50)
Tarsadenitis	100.0 (1/1)
Keratitis	100.0 (5/5)
Corneal ulcer	100.0 (13/13)
Trachomatis conjunctivitis	97.7 (42/43)***

*A subject with multiple diseases was counted as 1 subject per disease.

**Excluding *Chlamydia trachomatis* conjunctivitis

***Including subjects in unpublished papers

Clinical efficacy classified by bacterial strains detected at initial diagnosis (internally collected upon approval)

Bacterial strain	Efficacy rate* (%)
Staphylococcus sp.	93.1 (54/58)
Streptococcus sp.	100.0 (12/12)
Streptococcus pneumoniae	75.0 (3/4)
Enterococcus sp.	100.0 (2/2)
Micrococcus sp.	100.0 (1/1)
Moraxella sp.	100.0 (6/6)
Corynebacterium sp.	100.0 (13/13)
Klebsiella sp.	100.0 (2/2)
Serratia sp.	100.0 (1/1)
Providencia sp.	100.0 (1/1)
Haemophilus influenzae	100.0 (5/5)
Pseudomonas sp.	100.0 (10/10)
Pseudomonas aeruginosa	100.0 (3/3)
Burkholderia cepacia	100.0 (1/1)
Stenotrophomonas(Xanthomonas) maltophilia	100.0 (4/4)
Chlamydia trachomatis	97.7 (42/43)**

*A subject with multiple bacterial strains was counted as 1 subject per bacterial strain.

**Including subjects in unpublished papers

5.2. Pharmacokinetic properties

1) Blood concentrations

An appropriate amount of Tarivid ophthalmic ointment was applied to the both eyes 16 times every 30 minutes in healthy adult volunteers. The blood concentrations of ofloxacin were 0.009 μg/mL or less at 30 minutes after the last application.

2) Ocular distribution in animals

The peak levels of ofloxacin in the bulbar conjunctiva and the sclera were 9.72 μg/g and 1.61 μg/g, respectively in albino rabbits at 5 minutes after a single ocular application of about 40 mg ophthalmic ointment and thereafter gradually decreased. The peak levels of ofloxacin in the aqueous humor and the cornea were 0.69 μg/mL and 4.87 μg/g, respectively at 1 hour post-dose and thereafter decreased rapidly.

When one drop of 0.3% ophthalmic solution of levofloxacin, an optical isomer of ofloxacin (*l*-form), was applied to the eye of beagle dogs 4 times a day for 2 weeks, the concentrations of levofloxacin at 24 hours after the last administration were 39.4 μg/g in the iris-ciliary body and 12.3 μg/g in the choroid-retinal pigment epithelium, indicating the high distribution in the melanin-containing ocular tissues. On the other hand, the distribution of levofloxacin to the retinal tissues except the pigment epithelium was slight.

5.3. Pre-clinical safety data

1) Acute toxicity

Animal	Route of	LD50 (mg/kg)

Species	Administration	Male	Female
Mouse	p.o. i.v. s.c.	5,450 208 >10,000	5,290 233 >10,000
Rat	p.o. i.v. s.c.	3,590 273 7,070	3,750 276 9,000
Dog	p.o. i.v.	>200 >70	
Monkey	p.o.	500～1,000	–

p.o.: per os, i.v.: intravenous injection, s.c.: subcutaneous injection

2) Ocular irritation

No ocular irritation was observed when about 40 mg of this product and light-degraded product were applied to the eyes 10 times a day at 1-hour intervals in beagle dogs. No ocular irritation and toxicity were observed when about 40 mg of this product was applied to the eyes 3 times a day at 3-hour intervals for 3 months in beagle dogs.

3) Antigenicity

Ofloxacin had no antigenicity in systemic anaphylaxis, passive cutaneous anaphylaxis (PCA), passive hemagglutination, gel precipitation, and maximization tests in guinea pigs, PCA and passive hemagglutination tests in rabbits, and the detection test of specific IgE antibody formation in mice.

6. Pharmaceutical Particulars

6.1. List of excipients

Purified lanolin, Liquid paraffin, White petrolatum

6.2. Incompatibilities

None known

6.3. Shelf-life

36 months

Tarivid ophthalmic ointment should be used no longer than 1 month after first opening the aluminum tube.

6.4. Special precautions for storage

Do not store above 30˚C in a tight container.

6.5. Nature and contents of containers

Aluminum tube with polyethylene cap

Box of one tube of 3.5 g

7. Marketing Authorization Holder

Manufactured by:
Santen Pharmaceutical Co., Ltd.
Shiga plant, Shiga, Japan

Imported by:
Santen (Thailand) Co., Ltd.
Bangkok, Thailand

8. Marketing Authorization Number

1C XX/XX

9. Date of First Authorization

XX/XXXX

10. Date of Revision of the text

12/2019
(Approved date:……..)