002540

Broad-spectrum antibacterial ophthalmic solution

Cravit® ophthalmic solution 1.5% w/v

(Levofloxacin hydrate 1.5%)

Santen

DESCRIPTION

1) Pharmaceutical Dosage Form

Ophthalmic Solution

2) Qualitative and quantitative composition

i. Qualitative Declaration

Levofloxacin hydrate is a fluoroquinone antibacterial active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens. Levofloxacin hydrate, is the L-isomer of the racemate ofloxacin, has almost two times more potent antibiotic activity than ofloxacin.

ii. Quantitative Declaration

This product is a clear, pale yellow to yellow, sterile aqueous ophthalmic solution. Its pH is 6.1 - 6.9 and its osmolar ratio is 1.0 - 1.1.

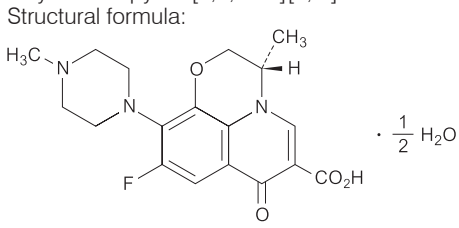
3) Pharmaceutical Form

Nonproprietary name: Levofloxacin Hydrate

Abbreviation: LVFX

Chemical Name: (3*S*)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*- pyrido[1,2,3-*de*][1, 4] benzoxazine-6-carboxylic acid hemihydrate

Structural formula:



Molecular formula: $C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$

Molecular weight: 370.38

Levofloxacin hydrate occurs as light yellowish white to yellowish white crystals or crystalline powder.

It is freely soluble in acetic acid (100), sparingly soluble in water and in methanol, slightly soluble in ethanol (99.5). It is freely soluble in 0.1 mol/l hydrochloric acid.

A light dark yellowish white gradually develops by light.

Melting point:Approx. 226°C (with decomposition)

INDICATIONS

<Indicated bacteria>

Susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Streptococcus pneumoniae*, *Enterococcus* sp., *Micrococcus* sp., *Moraxella* sp., *Corynebacterium* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Haemophilus influenzae*, *Haemophilus aegyptius* [Koch-Weeks bacillus], *Pseudomonas* sp., *Pseudomonas aeruginosa*, *Acinetobacter* sp., and *Propionibacterium acnes*.

<Indications>

Blepharitis, dacryocystitis, hordeolum, conjunctivitis, tarsadenitis, keratitis (including corneal ulcer), and postoperative infections.

<Precautions related to Indications>

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) The efficacy of this product to methicillin-resistant *Staphylococcus aureus* (MRSA) has not been proven. Therefore, other drug having a potent anti-MRSA activity should be administered immediately to patients positively infected with MRSA and not showing any improvement of symptoms with this product.

DOSAGE AND ADMINISTRATION

Usually, instill 1 drop a time to the eye 3 times daily. The dosage may be adjusted according to the patient's symptoms.

CONTRAINDICATIONS (This product is contraindicated in the following patients.)

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

PRECAUTIONS

1.Adverse Reactions

Adverse reactions (treatment-related adverse events) were reported in 7 of 238 patients (2.9%) and in 1 of 8 healthy subjects (12.5%) in clinical trials in Japan. The adverse reactions were eye irritation in 3 patients (1.3%), dysgeusia in 2 patients (0.8%) and 1 healthy subject (12.5%), eye itching in 1 patient (0.4%), and urticaria in 1 patient (0.4%).

i. Clinically significant adverse reactions

Shock, anaphylactoid reaction (incidences unknown) : Since shock and anaphylactoid reaction 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.

ii. Other adverse reactions

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

Type \ Incidence	Incidence unknown	5% > ≥0.1%
Hypersensitivity	Blepharitis (redness of eyelid / eyelid oedema, etc.), dermatitis eyelid, rash	Urticaria, itching
Ophthalmic	Corneal disorder including keratitis superficial diffuse etc., conjunctivitis (conjunctival hyperaemia / conjunctival oedema, etc.), eye pain, corneal deposits	Irritation
Others	–	Dysgeusia (Taste bitter, etc.)

2.Pediatric Use

The safety of this product to low birth weight infants, neonates, infants or children has not been established. (No clinical experience with low birth weight infants, neonates or infants. Limited clinical experience with children).

3.Precautions concerning Use

1) Route of administration: Ophthalmic use only.
2) At the time of administration:
   i. Instruct the patient to be careful not to touch the tip of the bottle to the eye directly in order to avoid contamination of the drug.
   ii. When more than one ophthalmic drug is used, at least 5 minutes of intervals should be taken.

4.Interaction with other medicinal products and other forms of interactions

Not specified.

5.Pregnancy and lactation

This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits are judged to outweigh the possible risks associated with treatment. [The safety of this product during pregnancy has not been established.]

6.Effects on ability to drive and use machine

Not specified.

7.Overdose

Not specified

参天製薬　クラビット点眼液1.5%（シンガポール）添付文書〈03〉ﾅﾁｭ　420×120　1°コン　大光印刷株式会社（20/08/20）
757106

Approved 09-Nov-2020 09-31 UTC

PHARMACOLOGICAL PROPERTIES

1.Pharmacodynamic properties

Levofloxacin hydrate, is the L-isomer of the racemate ofloxacin, has almost two times more potent antibiotic activity than ofloxacin.

i. ATC classification

Pharmacotherapeutic group: Sensory Organs - Ophthalmologicals - Antiinfectives - Antibiotics
ATC code: S01AE05.

ii. Mechanism of action

Main mechanism of action of levofloxacin hydrate is to inhibit bacterial DNA synthesis by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV activities. It depends on the bacteria strain as to how much potency is exerted: against DNA gyrase (topoisomerase II) or topoisomerase IV.

iii. Antibacterial activity

Antibacterial activity

Levofloxacin hydrate exerts a broad-spectrum potent antibacterial activity *in vitro* against organisms causing ophthalmological infections, including gram-positive bacteria (*Staphylococcus* sp., *Streptococcus* sp. [including *S. pneumoniae*], *Micrococcus* sp., *Enterococcus* sp., *Corynebacterium* sp., etc.), gram-negative bacteria (*Pseudomonas* sp. [including *P. aeruginosa*], *Haemophilus influenzae*, *Moraxella* sp., *Serratia* sp., *Klebsiella* sp., *Proteus* sp., *Acinetobacter* sp., *Enterobacter* sp. etc.), and anaerobic bacteria (*Propionibacterium acnes*, etc.).

Impact of dosage on emergence of levofloxacin resistance

In studies using *in vitro* ocular tissue concentration simulation model, this product, instilled 3 times daily was more effective than 0.5% product, in preventing the emergence of the levofloxacin-resistant methicillin-susceptible *Staphylococcus aureus* strain (HSA201-00027, levofloxacin MIC: 0.5 μg/mL) and the levofloxacin-resistant *P. aeruginonosa* strain (HSA201-00094, levofloxacin MIC: 1 μg/mL). Both of this product and 0.5% product, prevented the emergence of levofloxacin-resistant methicillin-susceptible coaglase-negative *Staphylococci* strain (HSA201-00039, levofloxacin MIC: 0.25 μg/mL).

2.Pharmacokinetic properties

i. Plasma concentration

Levofloxacin concentration in plasma was measured in 8 healthy adult volunteers during 8-day course of treatment with this product, bilateral instillation at one drop/eye/time, once daily for Day 1 and 8 times daily for 7 days (from Day 2 – 8). On Day 8, the mean maximum levofloxacin concentration of 24.1 ng/mL was measured after 26 minutes of the last instillation.

ii. Ocular distribution in animals (white rabbit)

Fifty μL of this product were ocular instilled once in the right eyes of rabbits. The mean maximum levofloxacin concentration of 32.5 μg/g in cornea was measured after 15 minutes of the instillation, and then levofloxacin concentration in cornea gradually decreased with half-life of 86 minutes. The mean maximum levofloxacin concentration of 14.7 μg/g in bulbar conjunctiva and palpebral conjunctiva was measured after 15 minutes of the instillation, and then levofloxacin concentration in bulbar conjunctiva and palpebral conjunctiva slightly rapidly decreased by 1 hour. The mean maximum levofloxacin concentration of 3.1 μg/mL in aqueous humor was measured after 30 minutes of the instillation, and then levofloxacin concentration in aqueous humor gradually decreased with half-life of 71 minutes.

3.Preclinical safety data

Ocular toxicity of levofloxacin (LVFX) ophthalmic solutions was evaluated in various regimens using albino or pigmented rabbits.

Ocular irritation of LVFX ophthalmic solutions was assessed at concentrations up to 25% after 10 repeated instillations in a single day at 30-minute intervals using albino rabbits. Ocular irritation was noted at 10% or higher, but not at 3.0% or lower.

Ocular toxicity of LVFX ophthalmic solutions was evaluated after 2 weeks instillations to the eyes of albino rabbits at concentrations up to 1.0%, and 4 and 26 weeks instillations to the eyes of pigmented rabbits at concentrations up to 3.0%. No evidences of ocular toxicity were observed in these studies.

Skin sensitization and skin photosensitization studies indicate that LVFX topically applied to the skin of guinea pigs is not immunogenic and photosensitizing.

Ocular safety of light-exposed and light-degraded LVFX ophthalmic solutions was assessed by 1 day ocular irritation study, since the reduction in LVFX content and production of degraded substance were recognized when LVFX ophthalmic solution was exposed to light in stressed condition. The light-induced degraded substances produced no abnormalities in the eyes.

PHARMACEUTICAL PARTICULARS

1.List of excipients

Inactive ingredient: Concentrated glycerin, dilute hydrochloric acid and sodium hydroxide

2.Incompatibilities

None known

3.Shelf life

3 years (36 months)
After first opening: to be used within one month.

4.Special precautions for storage

Store at or below 30 °C in a tight container under protection from light.

5.Nature and contents of container

5mL plastic bottle, 1 bottle per box

6.Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

Manufactured by
SANTEN PHARMACEUTICAL CO., LTD.
Noto plant: 2-14, Shikinami, Hodatsushimizu-cho, Hakui-gun, Ishikawa, Japan.

Licensed by
DAIICHI SANKYO CO., LTD.
3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

DATE OF REVISION OF THE TEXT
July 2020

1CV-SG
03