Bar prints 100mm @ 100%

Santen | **COMMERCIAL ARTWORK**

Description:	Cravit 1.5% (MY) 5 ml Leaflet
CMO Item Number:	N/A
CMO SPEC Number:	N/A
GLAMS Part Number:	CAW-5939-01
Technical Drawing No:	N/A
Dimension:	420 X 120 mm
Pharma Code:	001691
2D matrix:	N/A
Date:	12-05-2023
Market:	MY
Material Code:	752817
Artwork Version Number:	03
Schawk Job No.:	108690224/403295166

Printable Colours:

Santen PI Blue

Non Print:

Profile Technical Info

SGK is a Matthews International Corporation

Cravit®1.5% ophthalmic solution

(Levofloxacin Hydrate 1.5%)

75281703

001691

Santen

Product description

Levofloxacin hydrate is a fluoroquinolone 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. Levofloxacin hydrate is a clear, pale yellow to yellow sterile aqueous ophthalmic solution.

Indications

For the treatment of bacterial conjunctivitis caused by susceptible strains of the designated microorganisms.

<Indicated bacteria>
Susceptible strains of *Staphylococcus sp*., *Streptococcus sp*., *Streptococcus pneumoniae*, *Enterococcus sp*., *Corynebacterium sp*., *Klebsiella sp*., *Enterobacter sp*., *Serratia sp*., *Proteus sp*., *Haemophilus influenzae*, *Haemophilus aegyptius [Koch-Weeks bacillus]*, *Acinetobacter sp*., *and Propionibacterium acnes*.

Dosage and Administration

Instill 1 drop in the affected eye(s) 3 times daily.

Contraindications

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

Warning and Precautions

1.Precautions

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 proved. 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.

2.Adverse drug Reactions

Adverse reactions were reported in 7 of 238 patients (2.9%) in clinical trials in Japan. The adverse reactions were eye irritation in 3 patients (1.3%), dysgeusia in 2 patients (0.8%), eye itching in 1 patient (0.4%), and urticaria in 1 patient (0.4%).

1) Clinically significant adverse drug reactions

Shock, anaphylactoid reaction (incidences unknown) : Since shock and anaphylactoid reaction may occur on levofloxacin ophthalmic solution 0.5% (0.5% product), 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 drug 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.)

*Incidences are unknown because these adverse reactions were observed only on 0.5% product or in countries other than Japan.

3.Use during Pregnancy, Delivery or 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.]

4.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.)

5.Precautions concerning Use

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

6.Interaction of other medicaments

No particularly specified

7.Overdose and treatment

No particularly specified

Pharmacodynamics/Pharmacokinetics

1.Pharmacodynamics

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

1) 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.

2) 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.Pharmacokinetics

1) Plasma concentrations

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 maximum levofloxacin concentration of 24.1 ng/mL was measured after 26 minutes of the last instillation.

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2) Ocular distribution in animals (white rabbit)

Fifty μL of this product were ocular instilled once in the right eyes of rabbits. The 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 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 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.

Clinical Studies

Efficacy by diagnosis

The effectiveness rates of Cravit 1.5% ophthalmic solution by diagnosis in open label Phase III study conducted on 176 patients with bacterial conjunctivitis and bacterial keratitis are summarized below.

Disease	Effectiveness rate (%) ["effective" or better evaluations]			
	1.5 % (this product)		0.5 %§ (for reference)	
Blepharitis	–		93.3	(14/15)
Dacryocystitis	–		87.5	(28/32)
Hordeolum	–		92.5	(37/40)
Conjunctivitis	100.0	(170/170)	91.6	(196/214)
Tarsadenitis	–		95.2	(20/21)
Keratitis (including corneal ulcer)	100.0	(6/6)	93.8	(30/32)

Note) § Patients with multiple diseases were counted as one case per disease.

Efficacy by organism susceptible to levofloxacin

The effectiveness rates in the above 176 patients classified by the causative organisms are listed below.

Organism	Effectiveness rate§ (%) ["effective" or better evaluations]			
	1.5 % (this product)		0.5 % (for reference)	
Staphylococcus sp.	100.0	(98/98)	91.8	(157/171)
Streptococcus sp.	100.0	(10/10)	95.8	(23/24)
Streptococcus pneumoniae	100.0	(25/25)	94.7	(18/19)
Enterococcus sp.	100.0	(4/4)	87.5	(7/8)
Micrococcus sp.	–		100.0	(2/2)
Moraxella sp.	–		85.7	(12/14)
Corynebacterium sp.	100.0	(79/79)	86.2	(25/29)
Klebsiella sp.	100.0	(2/2)	85.7	(6/7)
Enterobacter sp.	100.0	(2/2)	100.0	(4/4)
Serratia sp.	100.0	(2/2)	100.0	(3/3)
Proteus sp.	100.0	(2/2)	75.0	(3/4)
Morganella morganii	–		100.0	(4/4)
Haemophilus influenzae	100.0	(17/17)	100.0	(10/10)
Pseudomonas sp.	–		100.0	(7/7)
P. aeruginosa	–		100.0	(5/5)
Stenotrophomonas (Xanthomonas) maltophilia	–		80.0	(4/5)
Acinetobacter sp.	100.0	(1/1)	94.1	(16/17)
Propionibacterium acnes	100.0	(13/13)	93.0	(40/43)

Note) § When multiple causative organisms were detected in patients, each organism was counted as one case.

Efficacy on aseptic treatment during a perioperative period for ocular surgery

(data on Cravit 0.5% , for reference)

As the result of evaluation of preoperative aseptic effect of Cravit 0.5% on patients before ophthalmic operation, the aseptic ratio was 70% (35/50).

Storage condition

Store below 30°C. Protect from light. After first opening: to be used within one month.

Dosage form and package available

Ophthalmic solution

5mL, 1 plastic bottle per box

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

Product Registration Holder
SANTEN PHARMA MALAYSIA SDN. BHD. (1117719-T)
Unit #23A-10, Q Sentral,
No. 2A, Jalan Stesen Sentral 2, Kuala Lumpur Sentral,
50470 Kuala Lumpur, Malaysia.

Date of Revision
May 2019

1CV-MLS
03

Approved 15-May-2023 06-06 UTC

Username	Full Name	Status	Date/Time (UTC)
GaithriGanesan	Gaithri Ganesan	Approved	12-May-2023 07-56 UTC
VonnyHuang	Vonny Huang	Approved	12-May-2023 08-07 UTC
KahPeiLau	Kah Pei Lau	Approved	12-May-2023 08-26 UTC
GraceLou	Grace Lou	Approved	12-May-2023 08-27 UTC
CalvinLow	Calvin Low	Approved	15-May-2023 05-57 UTC
KazuhiroNishino	Kazuhiro Nishino	Approved	15-May-2023 06-06 UTC