Summary of Product Characteristics

1 NAME OF THE MEDICAL PRODUCT

CRAVIT I.V.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mL, 100 mL and 150 mL. bottle of Cravit i.v. solution for infusion contains 250 mg 500 mg and 750 mg of levofloxacin (5 mg/mL).

3 PHARMACEUTICAL FORM

Solution for infusion.

The appearance of Cravit i.v. may range from a clear yellow to a greenish-yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cravit i.v. is indicated for the treatment of adults (≥16 years of age) with mild, moderate and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below, when intravenous administration offers a route of administration advantageous to the patient (e.g. patient cannot tolerate an oral dosage form). Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Community-acquired pneumonia due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila* or *Mycoplasma pneumoniae.*

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,* or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β -lactam is recommended.

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus* or *Streptococcus pyogenes.*

Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes* or *Proteus mirabilis.*

Urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* or *Staphylococcus saprophyticus.*

Pyelonephritis (mild to moderate) caused by *Escherichia coli.*

4.2 Posology and method of administration

Cravit i.v. should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen. The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Cravit i.v. should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. It is usually possible to switch from initial intravenous treatment to the oral route after a few days. The usual dose is 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as described in the following dosing chart.

Patient with normal renal function *(CL_{CR} > 80 mL/min)**:***

Infection	Unit Dose	Freq.	Duration	Daily Dose
Comm. Acquired pneumonia	500 mg	q 24 h	7-14 days	500 mg
Comm. Acquired pneumonia	750 mg	q 24 h	5 days	750 mg
Nosocomial Pneumonia	750 mg	q 24 h	7-14 days	750 mg
Uncomplicated SSTI	500 mg	q 24 h	7-10 days	500 mg
Complicated SSTI	750 mg	q 24 h	7-14 days	750 mg
Urinary Tract Infection	250 mg	q 24 h	10 days	250 mg
Complicated Urinary Tract Infection	750 mg	q 24h	5 days	750 mg
Pyelonephritis	250 mg	q 24 h	10 days	250 mg
Acute Pyelonephritis	750 mg	q 24h	5 days	750 mg

Patients with impaired renal function:

Renal Status	Initial Dose	Subsequent Dose

Comm. Acquired Pneumonia / Uncomplicated SSSI

CL_{CR} from 50 to 80 mL/min	No dosage adjustment required		
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg	q 24 h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg	q 48 h
Hemodialysis	500 mg	250 mg	q 48 h
CAPD	500 mg	250 mg	q 48 h

Comm. Acquired Pneumonia / Nosocomial Pneumonia / Complicated SSSI

CL_{CR} from 50 to 80 mL/min	No dosage adjustment required		
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg	q 48 h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg	q 48 h
Hemodialysis	750 mg	500 mg	q 48 h
CAPD	750 mg	500 mg	q 48 h

Complicated UTI / Pyelonephritis

CL_{CR} ≥ 20 mL/min	No dosage adjustment required		
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg	q 48 h

CL_{CR} = *creatinine clearance*

CAPD = chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

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 causative bacteria to this drug has been confirmed, in order to prevent emergence of drug resistant-bacteria.

Special population

Careful administration should be considered in the following patients group:

Patients with impaired liver function

No adjustment of dosage is required since levofloxacin is not metabolized to any relevant extent by liver and is mainly excreted by kidney.

Patients with impaired renal function

Blood concentrations of levofloxacin are sustained in patients with renal dysfunction. It is advisable, therefore, that the dose be reduced and the dosing interval lengthened is required [see Posology and method of administration]

Pediatric patients

As the safety and effectiveness of levofloxacin in low birth weight infants, new born infants, infants or children and adolescents below the age of 16 years has not been established, levofloxacin should not be administrated in pediatric patients. In animal studies, arthropathy was noted [in juvenile dogs, young adult dogs (13-month-old), and juvenile rats]

Geriatric patients

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

For compatibility and incompatibility with other infusion solution see Incompatibilities

4.3 Contraindications

Levofloxacin is contraindicated in the following patients:

1. Patients with a history of hypersensitivity to levofloxacin, ofloxacin or any excipients of this product
2. Patients with epilepsy
3. Patients with history of tendon disorder related to fluoroquinolones administration
4. Children or adolescents below the age of 16 years
5. Pregnant women or women suspected of being pregnant

6. Breast-feeding women

4.4 Special warnings and precautions for use

Cravit i.v. should be administered with caution in the following patients:

1. Patients with severe renal impairment

   Levofloxacin is excreted mainly by the kidneys and persistence of high serum level in patients with renal impairment has been reported.

2. Patients with known or suspected CNS disorder such as epilepsy or with a history of convulsive diseases that may predispose to seizures or lower the seizure threshold, convulsion may occur.

3. Diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (especially, sulfonylureas) or with insulin preparations.

4. Patients with a history of hypersensitivity to quinolone antibiotics.

5. Patients with serious heart diseases (e.g. arrhythmia and ischemic heart disease) ,patients with uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia) and patients receiving Class IA and III antiarrhythmic agents. QT prolongation may occur. (see section "SERIOUS ADVERSE REACTIONS" AND "Interaction with other medicinal products and other forms of interaction ")

6. Patients with myasthenia gravis

   Levofloxacin may cause exacerbation of myasthenia gravis symptom.

7. Geriatric patients.

   Since renal function is generally depressed in geriatric patients and levofloxacin is excreted mainly by the kidneys, levofloxacin should be used with caution in this population. It has been reported that tendon disorders are more likely to occur. (see section Posology and method of administration**"**)

8. Rapid or bolus intravenous injection may result in hypotension. Cravit i.v. should only be administered by slow intravenous infusion over a period of 60 minutes or 90 minutes.

9. Levofloxacin is more soluble than other quinolones; adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of highly concentrated urine.

10. Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis*, and therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.
11. Some undesirable effects (see ADVERSE REACTIONS) may impair the patient's ability to concentration and react, and therefore may constitute a risk in situation where these abilities are of special importance (e.g. driving a car or operating machinery).
12. Excessive exposure to sunlight should be avoided. However, phototoxicity has been observed very rare: incidence < 0.01%. Therapy should be discontinued if phototoxicity (e.g. a skin eruption) occurs.
13. Patients complicated with aortic aneurysm or aortic dissection, or patients who have a previous history, positive family history, or risk factors (Marfan syndrome, etc.) of aortic aneurysm or aortic dissection [The increased risk of aortic aneurysm and dissection after intake of fluoroquinolones have been reported in overseas epidemiologic studies (see "SERIOUS ADVERSE REACTION")]
14. Aortic aneurysm or aortic dissection may occur; there-fore, patients should be carefully observed and instructed to seek medical attention immediately if they experience symptoms, e.g. in case of pain in the abdomen, chest, or back. Imaging assessment should be considered if necessary, for patients complicated with aortic aneurysm or aortic dissection, or patients who have a previous history, positive family history, or risk factors of aortic aneurysm or aortic dissection (see "SERIOUS ADVERSE REACTION").

SERIOUS ADVERSE REACTION

The following serious adverse reactions have been reported in patients receiving therapy with levofloxacin. If the following reactions are suspected, treatment with levofloxacin should be discontinued immediately and appropriate therapeutic measure should be taken.

1. Shock or anaphylactoid reaction (initial symptoms: erythema, rigor, dyspnea, etc.)
2. Toxic epidermal necrolysis (TEN) or oculomucocutaneous syndrome (Stevens-Johnson syndrome)
3. Convulsion

4. QT prolonged and ventricular tarchycardia (including Torsades de pointes): During post-marketing surveillance, prolonged QT which may sometimes lead to the occurrence of ventricular tachycardia including torsades de pointes have been reported spontaneously in patients taking levofloxacin. The risk of the events may be increased in patients with serious heart diseases (e.g. arrhythmia and ischemic heart disease), patients with uncorrected hypokalemia, patients receiving Class IA (quinidine sulfate, procainamide hydrochloride) and Class III (amiodarone hydrochloride, sotalol hydrochloride) antiarrhythmic agents and in geriatric patients.

5. Acute renal failure or interstitial nephritis

6. Hepatitis fulminant, hepatic function disorder or jaundice (initial symptoms: nausea, vomiting, anorexia, malaise, pruritus, etc.)

7. Pancytopenia, agranulocytosis (initial symptoms: pyrexia, pharynx pain, malaise, etc.), hemolytic anemia with hemoglobinuria or thrombocytopenia

8. Interstitial pneumonia or eosinophilic pneumonia accompanied with pyrexia, cough, dyspnea, abnormal chest X-ray, or eosinophilia, etc.

9. Serious colitis with bloody stool, such as pseudomembranous colitis: If such symptoms as abdominal pain and frequent diarrhea are noted, treatment with levofloxacin should be discontinued immediately and appropriate therapeutic measures taken.

10. Rhabdomyolysis characterized by myalgia, weakness, elevated CK (CPK) and increased myoglobin in plasma and urine, etc., and accompanied with acute exacerbation of renal function.

11. Dysglycemia: During post-marketing surveillance, hypoglycemia and hyperglycemia have been reported in patients taking levofloxacin. Serious symptoms such as hypoglycemic coma have been reported in patients receiving levofloxacin. Hypoglycemia may be prone to develop in patients with diabetes mellitus (especially, those receiving sulfonylureas or insulin preparations), patients with impaired renal function and geriatric patients.

12. Tendon disorders such as Achilles tendonitis or tendon rupture: If symptoms such as pain, edema in the peritendinous region, and redness around the tendon are observed, treatment with levofloxacin should be discontinued immediately and appropriate therapeutic measures taken. The risk of tendonitis and tendon rupture is increased in those over age 60, in those on concomitant corticosteroid therapy, and transplant recipients.

13. Psychiatric symptoms such as confusion, delirium and depression

14. Hypersensitivity vasculitis: If symptoms such as pyrexia, abdominal pain, arthralgia, purpura or maculopapules, and skin biopsy evidence of leukocytoclastic vasculitis are observed, treatment with levofloxacin should be discontinued immediately and appropriate therapeutic measures taken.

15. Exacerbation of myasthenia gravis.

16. Aortic aneurysm, aortic dissection (incidence unknown): Aortic aneurysm or aortic dissection may occur. If any abnormalities are observed, appropriate medical treatment should be taken. (see **"**Special warnings and precautions for use**"**)

17. Peripheral neuropathy (incidence unknown[Note 1)]): Peripheral neuropathy may occur. If symptoms such as numbness, muscleweakness, or pain are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Note1) The incidence of adverse reactions is unknown as these adverse reactions are those which have been reported with preparation containing the same active ingredients or have been reported overseas.

4.5 Interaction with other medicinal products and other forms of interaction

Antacid, Sucralfate, Metal Cations and Multivitamins:

There are no data concerning an interaction of intravenous quinolones with oral antacid, sucralfate, multivitamins, or metal cation. However, no quinolones should be co-administered with any solution containing multivitamin cation, e.g. magnesium, through the same intravenous line.

Theophylline, Fenbufen, or similar non-steroidal anti-inflammatory drugs (phenylacetic acid/propionic acid derivatives):

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However there are indications of a pronounced lowering of the cerebral seizure threshold when quinolones are given concurrently with other drugs that lower the seizure threshold (e.g. theophylline) or with fenbufen or similar non-steroidal anti-inflammatory drugs.

Antidiabetic agents:

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Anticoagulant drug (warfarin and its derivatives)

Coadministration with warfarin and its derivatives has been reported that the effect of warfarin was potentiated (hepatic metabolism of warfarin may be inhibited, or free warfarin may be increased by competitive displacement from the protein binding site) and therefore prothrombin time prolonged.

Class IA antiarrhythmics and Class III antiarrhythmics

Levofloxacin should be used with caution in patients receiving drug known to cause QT prolonged, Class IA antiarrhythmics (e.g. quinidine sulfate and procainamide hydrochloride), Class III antiarrhythmics (e.g. amiodarone hydrochloride and sotalol hydrochloride) QT prolongation may occur.

Corticosteroids (oral agents and injections)

Coadministration with corticosteroids has been reported that the risk of tendon disorders is increased. The use of levofloxacin in combination with corticosteroids should be initiated only when the therapeutic benefits outweigh the risks.

4.6 Fertility, pregnancy and lactation

Use during pregnancy

Levofloxacin must not be used in pregnant women or women suspected of being pregnant since the safety of the product in pregnant women has not been established (see section "**CONTRAINDICATION**")

Use during lactation

Since ofloxacin is known to be excreted in breast milk, nursing mothers should be guided to avoid the breast-feeding during treatment with levofloxacin (see section "**CONTRAINDICATION**")

4.7 Effects on ability to drive and use machines

Neurologic adverse effects such as dizziness/vertigo and somnolence may occur. Therefore, patients should be instructed that such neurologic adverse effects may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situation where these abilities are of special importance (e.g. activities at high place, driving a car or operating machinery)

4.8 Undesirable effects

The following adverse reactions have been reported in clinical studies and post marketing experience. The incidence identified below reflects exposure to 500 mg tablet of levofloxacin in total of 1,930 patients in pooled Phase 3 and Phase 4 clinical trials (e.g., 1,582 patients from Phase 3 clinical trials conducted in Japan (337 patients) and China (1,245 patients) and 348 patients from Phase 4 clinical trials) or 29,880 patients in a post marketing studies conducted in Japan. If the incidence category of an adverse reaction is different between each source (i.e., the incidence from the pooled clinical trials and the incidence from the post marketing study), the higher frequency is represented.

The following CIOMS frequency rating is used:

Very common: 10% ≤ incidence

Common: 1% ≤ incidence < 10%

Uncommon: 0.1% ≤ incidence < 1%

Rare: 0.01% ≤ incidence < 0.1%

Very rare: incidence < 0.01%

*: see "**SERIOUS ADVERSE REACTIONS**", each incidence is based on serious reactions.

- **Blood and lymphatic system disorders**

  Common: anemia

  Very rare: thrombocytopenia*

  Incidence unknown: pancytopenia*, agranulocytosis*, hemolytic anemia with hemoglobinuria*

- **Immune system disorder**

  Incidence unknown: anaphylactoid reaction*

- **Metabolism and nutrition disorder**

  Uncommon: anorexia

Incidence unknown: hypoglycemia (hypoglycemic coma may occur)*, hyperglycemia*

- **Psychiatric disorders**

Common: sleep loss

Rare: hallucination

Incidence unknown: psychiatric symptoms such as confusion*, delirium*, depression*

- **Nervous system disorders**

Common: dizziness/vertigo, headache

Uncommon: somnolence, numbness, tremor, mental dullness, dysgeusia

Rare: consciousness disturbed

Very rare: convulsion*, ageusia

Incidence unknown: peripheral nerve disorder, extrapyramidal disorder, anosmia, parosmia

- **Eye disorders**

Rare: abnormal vision

- **Ear and labyrinth disorders**

Uncommon: tinnitus

Incidence unknown: hearing losses

- **Cardiac disorders**

Uncommon: palpitations

Incidence unknown: ventricular tachycardia (including Torsades de pointes)*, QT prolonged*, tachycardia

- **Vascular disorders**

Very rare: shock*

Incidence unknown: hypotension

- **Respiratory, thoracic and mediastinal disorders**

Uncommon: dry throat

Incidence unknown: interstitial pneumonia*, eosinophilic pneumonia*

- **Gastrointestinal disorders**

Common: nausea, vomiting, diarrhea, abdominal discomfort

Uncommon: abdominal pain, dyspepsia, abdominal distension, constipation

Rare: stomatitis

Very rare: glossitis

Incidence unknown:	colitis with bloody stool, such as pseudomembranous colitis*

- **Hepatobiliary disorders**

Uncommon:	hepatic function abnormal (severe hepatic function disorder* may rarely occur)
Incidence unknown:	hepatitis fulminant*, jaundice*

- **Skin and subcutaneous tissue disorders**

Uncommon:	pruritus, rash
Rare:	hyperhidrosis, urticaria
Very rare:	photosensitivity
Incidence unknown:	toxic epidermal necrolysis (TEN) *, oculomucocutaneous syndrome (Stevens-Johnson syndrome) *, hypersensitivity vasculitis*

- **Musculoskeletal and connective tissue disorders**

Uncommon:	arthralgia, pain in extremity, back pain, weakness
Rare:	arthropathy, myalgia
Incidence unknown:	rhabdomyolysis*, tendon disorders such as Achilles tendonitis or tendon rupture*, exacerbation of myasthenia gravis*, muscle rupture

- **Renal and urinary disorders**

Uncommon:	hematuria, urinary retention
Rare:	pollakiuria, oliguria, acute renal failure*
Incidence unknown:	interstitial nephritis*, anuria, dysuria

- **General disorders and administration site conditions**

Very common[#]:	infusion site reaction (erythema, pruritus, swelling, pain, induration, warmth, discomfort, phlebitis, vasculitis, angiopathy, puncture site pain) #: The incidence of the relevant event is based on data from Japan clinical studies in 586 patients intravenously treated with levofloxacin.
Uncommon:	thirst, chest discomfort, malaise, feeling hot, edema
Very rare:	pyrexia
Incidence unknown:	chest pain

- **Investigations**

Common: AST increased, ALT increased, LDH increased, white blood cell count decreased, eosinophil count increased

Uncommon: createnine increased, urinary protein positive, alkaline phosphatase increased, γ-GTP increased, blood bilirubin increased, lymphocyte count decreased, neutrophil count decreased, CPK increased, glucose urine present, blood glucose decreased, platelet count decreased

Rare: BUN increased, urine output decreased

Very rare: blood glucose increased

The events of which frequency category observed in Japanese clinical studies in 586 patients and post-marketing study in 1138 patients intravenously treated with levofloxacin is higher than the rating shown in this section (**ADVERSE REACTIONS**) is listed below.

- **Psychiatric disorders**

Uncommon: hallucination

- **Respiratory, thoracic and mediastinal disorders**

Uncommon: interstitial pneumonia*

- **Gastrointestinal disorders**

Common: constipation

Uncommon: glossitis

- **Hepatobiliary disorders**

Common: hepatic function abnormal (severe hepatic function disorder* may uncommon occur)

- **Musculoskeletal and connective tissue disorders**

Uncommon: myalgia

- **General disorders and administration site conditions**

Uncommon: pyrexia

- **Investigations**

Common: γ-GTP increased, alkaline phosphatase increased

4.9 Overdose

According to toxicity studies in animals, the most important signs to be expected following acute overdosage of Cravit i.v. solution for infusion are central nervous

system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, as well as gastrointestinal reactions such as nausea and mucosal erosions.

In the event of an acute overdosage, the stomach should be emptied. Antacid may be used for protection of gastric mucosa. No specific antidote exists. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

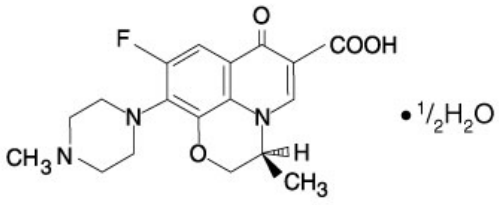
5.1 Pharmacodynamic properties

Nonproprietary name:Levofloxacin

Abbreviation: LVFX

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

Structural formula :



Molecular formula: $C_{18}H_{20}FN_3O_4 \bullet$ ½ H_2O

Molecular weight: 370.38

Melting point: 222 - 230 °C (decomposition)

Description: Light yellowish white to yellowish white crystals or crystalline powder, odorless and bitter taste. Freely soluble in glacial acetic acid, sparingly soluble in water and methanol, slightly soluble in ethanol, and practically insoluble in ether, Light sensitive.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. It is two folds stronger than that of ofloxacin. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involve inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for

DNA replication, transcription, repair and recombination. Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic gram-positive microorganisms

Enterococcus faecalis, Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus pneumoniae (including penicillin-resistant strains), *Streptococcus pyogenes*

Aerobic gram-negative microorganisms

Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa

Other microorganisms

Chlamydia pneumoniae, Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown.

Aerobic gram-positive microorganisms

Staphylococcus epidermidis, Streptococcus (Group C/F), Streptococcus (Group G), *Streptococcus agalactiae, Streptococcus milleri,* Viridans group streptococci

Aerobic gram-negative microorganisms

Acinetobacter anitratus , Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter Iwoffii, Bordetella pertussis, Citrobacter diversus, Citrobacter freundii, Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter sakazakii,

Klebsiella oxytoca, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas fluorescens, Serratia marcescens

Anaerobic gram-positive microorganisms

Clostridium perfringens

5.2 Pharmacokinetic properties

Absorption and serum concentration

Following a single 60 minutes and 90 minutes intravenous infusion of 500 mg and 750 mg of levofloxacin to healthy volunteers, the mean peak plasma concentration attained were 6.2 µg/mL and 11.5 µg/mL respectively. Levofloxacin pharmacokinetics is linear and predictable after single and multiple i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once daily dosage regimen. The peak and trough plasma concentrations attained following multiple once daily i.v. 500 mg regimens were approximately 6.4 and 0.6 µg/mL and 12.1 and 1.3 µg/mL after the 750 mg doses, respectively.

The plasma concentration profile of levofloxacin after i.v. administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and i.v. routes of administration can be considered interchangeable.

Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Penetration of levofloxacin into blister fluid is rapid and extensive. The blister fluid to plasma AUC ratio is approximately 1. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2 to 5 fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 µg/g over a 24 hour period after the single 500 mg oral dose.

In vitro, over the clinically relevant range (1 to 10 µg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and dose not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Sodium hydroxide, Hydrochloric acid

6.2 Incompatibilities

Cravit i.v. solution for infusion should not be mixed with heparin or alkaline solution (e.g. sodium hydrogen carbonate).

Compatibility

Cravit i.v. solution for infusion is compatible with the following solution for infusion:

0.9% Sodium Chloride Injection, USP

5% Dextrose Injection, USP

2.5% Dextrose in Ringer Solution

Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

6.3 Shelf life

Shelf-life as package for sale: indicated on the packaging

Shelf-life after removal of the outer packaging: 3 days

Shelf-life after perforation of the rubber stopper: 3 hours

6.4 Special precautions for storage

Protect from light

Keep out of the reach of children

Store below 30^{o}C

6.5 Nature and contents of container

50 mL, 100 mL and 150 mL. clear, ready for use solution in 50 mL, 100 mL and 150mL. glass bottle with a rubber stopper.

Boxes of 1 and 100 vials

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

NA

7 MARKETING AUTHORISATION HOLDER

M&H Manufacturing Co., Ltd.

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Under Authority of:

DAIICHI SANKYO (THAILAND) LTD. BANGKOK, THAILAND

Licensed by:

DAIICHI SANKYO CO., LTD. TOKYO, JAPAN

8 MARKETING AUTHORISATION NUMBER

CRAVIT I.V. Reg. No. xxxxxxxx

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: xxxxxxxx
Date of last renewal: xxxxxxxx

10 DATE OF REVISION OF THE TEXT

July 2021