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INSTRUCTION
for medical use

TIGERON®

Composition:
active substance: levofloxacin;
1 tablet contains levofloxacin hemihydrate equivalent to levofloxacin 500 mg or 750 mg;
excipients: povidone K29/32, microcrystalline cellulose, crospovidone, magnesium stearate, colloidal anhydrous silica, Opadry 03B84681 pink coating: hypromellose, titanium dioxide (E 171), polyethylene glycol, iron oxide red (E 172), iron oxide yellow (E 172).

Pharmaceutical form. Film-coated tablets.
Basic physico-chemical properties: pink coated capsule-shaped tablets, embossed "500" or 750" on one side.

Pharmacotherapeutic group.
Quinolone antibacterials. Fluoroquinolones. ATC code J01M A12.

Pharmacological properties.
Pharmacodynamics.
Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone group; it is S(-)enantiomer of the racemic mixture of the ofloxacin medicinal product.
Mechanism of action.
As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.
Ratio of pharmacokinetics/pharmacodynamics.
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).
Mechanism of resistance.
Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to levofloxacin.
Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.
Breakpoints.
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommended MIC breakpoints for levofloxacin, separating susceptible from increased exposure organisms and susceptible increased exposure from resistant organisms are presented in the below table for MIC testing (mg/l).

EUCAST clinical MIC breakpoints for levofloxacin (version 10.0; 2020-01-01).

Pathogen	Susceptible	Resistant
Enterobacteriacae	≤0.5 mg/l	>1 mg/l

Pseudomonas spp.	≤0.001 mg/l	>1 mg/l
Acinetobacter spp.	≤0.5 mg/l	>1 mg/l
Staphylococcus aureus Coagulase-negative staphylococci	≤0.001 mg/l	>1 mg/l
Enterococcus spp.[1]	≤4 mg/l	>4 mg/l
Streptococcus pneumoniae	≤0.001 mg/l	>2 mg/l
Streptococcus A, B, C, and G	≤0.001 mg/l	>2 mg/l
Haemophilus influenzae	≤0.06 mg/l	>0.06 mg/l
Moraxella catarrhalis	≤0.125 mg/l	>0.125 mg/l
Helicobacter pylori	≤1 mg/l	>1 mg/l
Aerococcus sanguinicola and urinae[2]	≤2 mg/l	>2 mg/l
Aeromonas spp.	≤0.5 mg/l	>1 mg/l
Pharmacokinetic-pharmacodynamic (non-species related) breakpoints	≤0.5 mg/l	>1 mg/l

[1] Uncomplicated urinary tract infections only
[2] Susceptibility can be inferred from ciprofloxacin susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive bacteria:
Bacillus anthracis, Staphylococcus aureus methicillin-susceptible, *Staphylococcus saprophyticus*, *Streptococci, group C* and *G*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*.
Aerobic Gram-negative bacteria:
Eikenella corrodens, Haemophilus influenzae, Haemophilus para-influenzae, Klebsiella oxytoca, Moraxella catarrhalis, Pasteurella multocida, Proteus vulgaris, Providencia rettgeri.
Anaerobic bacteria:
Peptostreptococcus.
Others:
Chlamydophila pneumoniae, Chlamydophila psittaci, Chlamidia trachomatis, Legionella pneumophila, Mycoplasma pneumoniae, Mycoplasma hominis, Ureaplasma urealyticum.

Species for which acquired resistance may be a problem
Aerobic Gram-positive bacteria:
Enterococcus faecalis, Staphylococcus aureus methicillin-resistant*, coagulase-negative *Staphylococcus spp.*
Aerobic Gram-negative bacteria:
Acinetobacter baumannii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Serratia marcescens.
Anaerobic bacteria:
Bacteroides fragilis.

Inherently Resistant Strains
Aerobic gram positive bacteria:
Enterococcus faecium.

* Methicillin-resistant *S. aureus* is very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

Pharmacokinetics.
Absorption.
Orally administered levofloxacin is rapidly and almost completely absorbed with C_{max} being obtained within 1–2 h. The absolute bioavailability is 99–100%.

Food has little effect on the absorption of levofloxacin.
Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.
Distribution.
Approximately 30–40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.
Penetration into tissues and body fluids.
Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebrospinal fluid.
Biotransformation.
Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for <5% of the dose and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.
Elimination.
Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (elimination half-life (t½): 6–8 h). Excretion is primarily by the renal route (>85% of the administered dose). The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175±29.2 ml/min). There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.
Linearity.
Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.
Subjects with renal insufficiency.
The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below.
Pharmacokinetics in renal insufficiency following single oral 500 mg dose:

Creatinine clearance (ml/min)	<20	20–49	50–80
Renal clearance (ml/min)	13	26	57
$t_{1/2}$ (hours)	35	27	9

Elderly subjects.
There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects, except those associated with differences in creatinine clearance.
Gender differences.
Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

Clinical characteristics.
Indications.
The drug is indicated in adults for the treatment of the following infections (see “Pharmacodynamics” and “Special warnings and precautions for use” sections):
- acute pyelonephritis and complicated urinary tract infections (see “Special warnings and precautions for use” section);
- chronic bacterial prostatitis;
- inhalation Anthrax: post-exposure prophylaxis and curative treatment (see “Special warnings and precautions for use” section).

For the below-mentioned infections the drug should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections:
- acute bacterial sinusitis;

- acute exacerbations of chronic obstructive pulmonary disease including bronchitis;
- community-acquired pneumonia;
- complicated skin and soft tissue infections;
- uncomplicated cystitis (see "Special warnings and precautions for use" section).

The drug may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Contraindications.
Hypersensitivity to levofloxacin, other quinolones or any excipient of the drug.
Epilepsy.
Patients with a history of tendon disorders related to fluoroquinolone administration.
Children's age under 18 years.
Pregnant women and breastfeeding women.

Interaction with other medicinal products and other kinds of interaction.
Effect of other medicinal products on levofloxacin
Iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine.
Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with levofloxacin tablets. Concurrent administration of fluoroquinolones with multivitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken 2 hours before or after levofloxacin tablet administration (see "Posology and method of administration" section). Calcium salts have a minimal effect on the oral absorption of levofloxacin.
Sucralfate.
The bioavailability of levofloxacin tablet is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin tablet administration (see "Special warnings and precautions for use" section).
Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs.
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold. Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.
Probenecid and cimetidine.
Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance. Caution should be exercised when levofloxacin is co-administered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.
Other relevant information.
Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.
Effect of levofloxacin on other medicinal products
Ciclosporin.
The half-life of ciclosporin was increased by 33% when co-administered with levofloxacin.
Vitamin K antagonists.
Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation

tests, therefore, should be monitored in patients treated with vitamin K antagonists see "Special warnings and precautions for use" section).
Drugs known to prolong the QT interval.
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic agents) (see "Special warnings and precautions for use" section).
Other relevant information.
In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.
Other forms of interactions
Food.
There is no clinically relevant interaction with food. The drug may therefore be administered regardless of food intake.

Special warnings and precautions for use.
The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see "Adverse reactions" section). Treatment of these patients with levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see "Contraindications" section).
Methicillin-resistant Staphylococcus aureus.
Methicillin-resistant *Staphylococcus aureus* (MRSA) is very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin.
Levofloxacin may be used in the treatment of acute bacterial sinusitis and acute exacerbation of chronic bronchitis when these infections have been adequately diagnosed.
Resistance to fluoroquinolones of *Escherichia coli* (the most common pathogen involved in urinary tract infections) varies across the different countries. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.
Inhalation Anthrax.
Use in humans is based on *in vitro Bacillus anthracis* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.
Prolonged, disabling and potentially irreversible serious adverse drug reactions.
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.
Tendinitis and tendon rupture.
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, in patients receiving daily doses of more than 1000 mg levofloxacin and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.
Myoclonus.
Cases of myoclonus have been reported in patients receiving levofloxacin (see "Adverse reactions" section). The risk of myoclonus is increased in the elderly and in patients with renal insufficiency unless

the levofloxacin dose is adjusted according to creatinine clearance. Levofloxacin should be discontinued immediately at the first appearance of myoclonus and appropriate treatment should be initiated.

Clostridium difficile-associated disease.

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of *Clostridium difficile*-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see "Adverse reactions" section). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately, and appropriate treatment initiated without delay.

Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizures.

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy (see "Contraindications" section) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline (see "Interaction with other medicinal products and other kinds of interaction" section). In case of convulsive seizures (see "Adverse reactions" section), treatment with levofloxacin should be discontinued.

Patients with glucose-6-phosphate dehydrogenase deficiency.

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment.

Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin should be adjusted in patients with renal impairment (see "Posology and method of administration" section).

Hypersensitivity reactions.

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see "Adverse reactions" section). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe cutaneous adverse reactions.

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin (see "Adverse reactions" section). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia.

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, occurring more frequently in the elderly, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended levofloxacin (see "Adverse reactions" section). Levofloxacin treatment should be stopped immediately if a patient reports blood glucose disturbance and alternative non-fluoroquinolone antibacterial therapy should be considered.

Prevention of photosensitisation.

Photosensitisation has been reported with levofloxacin (see "Adverse reactions" section). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists.

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be

monitored when these drugs are given concomitantly (see “Interaction with other medicinal products and other kinds of interaction” section).

Psychotic reactions.

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour, sometimes after only a single dose of levofloxacin (see “Adverse reactions” section). In the event that the patient develops these reactions, levofloxacin should be discontinued immediately at the first signs or symptoms of these reactions and patients should be advised to contact their prescriber for advice. Alternative non-fluoroquinolone antibacterial therapy should be considered, and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

QT interval prolongation.

Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome;
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics);
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesemia);
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations (see “Interaction with other medicinal products and other kinds of interaction”, “Posology and method of administration”, “Overdose”, and “Adverse reactions” sections).

Peripheral neuropathy.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with levofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see “Adverse reactions” section).

Hepatobiliary disorders.

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see “Adverse reactions” section). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis.

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post-marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders.

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see “Effects on ability to drive and use machines” and “Adverse reactions” sections).

Superinfection.

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory tests.

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence.

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones (see "Adverse reactions" section).
Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see "Adverse reactions" section).
Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or heart valve disease or in presence of other risk factors or conditions predisposing:

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome, or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis);
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome);
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.
Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.
Acute pancreatitis.
Acute pancreatitis may be observed in patients taking levofloxacin. Patients should be informed of the characteristic symptoms of acute pancreatitis. Patients experiencing nausea, malaise, abdominal discomfort, acute abdominal pain or vomiting should have a prompt medical evaluation. If acute pancreatitis is suspected, levofloxacin should be discontinued; if confirmed, levofloxacin should not be restarted. Caution should be exercised in patients with a history of pancreatitis (see "Adverse reactions" section).
Blood disorders
Bone marrow failure, including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia or agranulocytosis, may occur during treatment with levofloxacin (see "Adverse reactions" section). If any of these disorders are suspected, blood tests should be monitored. If abnormal results are obtained, discontinuation of levofloxacin should be considered.
Use during pregnancy and breastfeeding.
Pregnancy.
There is limited amount of data from the use of levofloxacin in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, in the absence of human data and due to that experimental data suggest risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women (see "Contraindications" sections).
Breastfeeding.
Levofloxacin is contraindicated in breastfeeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breastfeeding women (see "Contraindications" sections).
Fertility.
Levofloxacin caused no impairment of fertility or reproductive performance in rats.

Effects on ability to drive and use machines.
Levofloxacin has minor or moderate influence on the ability to drive and use machines. Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special

importance (e.g. driving a car or operating machinery).

Posology and method of administration.
The drug is administered once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.
The drug can also be used to complete the course of treatment in patients who have shown improvement during initial levofloxacin treatment intravenously. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.
Posology. The following dose recommendations can be given for the drug:

Dosage in patients with normal renal function (creatinine clearance >50 ml/min).

Indication	Daily dose regimen (according to severity)	Number of doses per day	Total duration of treatment (according to severity)
Acute bacterial sinusitis	500	1	10–14 days
Acute bacterial exacerbations of chronic obstructive pulmonary disease including bronchitis	500	1	7–10 days
Community-acquired pneumonia	500	1–2	7–14 days
Acute pyelonephritis	500	1	7–10 days
Complicated urinary tract infections	500	1	7–14 days
Uncomplicated cystitis	250*	1	3 days
Chronic bacterial prostatitis	500	1	28 days
Complicated skin and soft tissue infections	500	1–2	7–14 days
Inhalation Anthrax	500	1	8 weeks

* Since the tablet is not divisible, in the case of prescribing the drug in a dose of 250 mg or less, levofloxacin drugs with the possibility of such a dosage should be used.

Special populations
Patients with impaired renal function (creatinine clearance ≤50 ml/min)

Creatinine clearance, ml/min	Dose regimen		
	250* mg/24 h	500 mg/24 h	500 mg/12 h
50–20	*first dose:* 250* mg	*first dose:* 500 mg	*first dose:* 500 mg
	then: 125* mg/24 h	*then:* 250* mg/24 h	*then:* 250* mg/12 h
19–10	*first dose:* 250* mg	*first dose:* 500 mg	*first dose:* 500 mg
	then: 125* mg/48 h	*then:* 125* mg/24 h	*then:* 125* mg/12 h
10 (including haemodialysis and CAPD[1])	*first dose:* 250* mg	*first dose:* 500 mg	*first dose:* 500 mg
	then: 125* mg/48 h	*then:* 125* mg/24 h	*then:* 125* mg/24 h

* Since the tablet is not divisible, in the case of prescribing the drug in a dose of 250 mg or less, levofloxacin drugs with the possibility of such a dosage should be used.
[1] No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Patients with hepatic impairment. No adjustment of dose is required since levofloxacin is not metabolized to any relevant extent by the liver and is mainly excreted by the kidneys.
Older people. If renal function is not impaired, no dosage adjustment is required (see "Special warnings and precautions for use" section).
Paediatric population. Levofloxacin is contraindicated for children under 18 years (see "Contraindications" section).

Method of administration. Tablets should be swallowed without chewing and with sufficient amount of liquid. Tablets may be taken during meals or between meals. The drug should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium- or magnesium-containing buffering agents), and sucralfate administration, since reduction of absorption can occur (see "Interaction with other medicinal products and other kinds of interaction" section).
Paediatric population. Levofloxacin is contraindicated for children under 18 years (see "Contraindications" section).

Overdose.
Symptoms. The most important signs to be expected following acute overdose of levofloxacin are central nervous system symptoms such as confusion, myoclonus, hallucinations, tremors, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastrointestinal reactions such as nausea and mucosal erosions.
CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post-marketing experience.
Treatment. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

Adverse reactions.
Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Infections and invasions: uncommon – fungal infection including *Candida* infection, pathogen resistance.
Blood and lymphatic system disorders: uncommon – leukopenia, eosinophilia; rare – thrombocytopenia, neutropenia; not known – bone marrow failure, including aplastic anemia, pancytopenia, agranulocytosis, haemolytic anaemia.
Immune system disorders: rare – angioedema, hypersensitivity (see "Special warnings and precautions for use" section); not known – anaphylactic shock*, anaphylactoid shock* (see "Special warnings and precautions for use" section).
Endocrine system disorders: rare – syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
Metabolism and nutrition disorders: uncommon – anorexia; rare – hypoglycaemia, particularly in diabetic patients, hypoglycaemic coma (see "Special warnings and precautions for use" section); not known – hyperglycaemia (see "Special warnings and precautions for use" section).
*Psychiatric disorders***:* common – insomnia; uncommon – anxiety, confusional state, nervousness; rare – psychotic reactions (with e.g. hallucination, paranoia), depression, agitation, abnormal dreams, nightmares, delirium; not known – psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see "Special warnings and precautions for use" section), mania.
*Nervous system disorders***:* common – headache, dizziness; uncommon – somnolence, tremor, dysgeusia; rare – convulsion (see "Contraindications" and "Special warnings and precautions for use" sections), paraesthesia, memory impairment; not known – peripheral sensory neuropathy (see "Special warnings and precautions for use" section), peripheral sensory motor neuropathy (see "Special warnings and precautions for use" section), parosmia including anosmia, dyskinesia, extrapyramidal disorders, ageusia, syncope, benign intracranial hypertension, mioclonus.
*Eye disorders***:* rare – visual disturbances such as blurred vision (see "Special warnings and precautions for use" section); not known – transient vision loss (see "Special warnings and precautions for use" section), uveitis.
*Ear and labyrinth disorders***:* uncommon – vertigo; rare – tinnitus; not known – hearing impairment, hearing loss.
*Cardiac disorders***:* rare – tachycardia, palpitation; not known – ventricular tachycardia, which may result in cardiac arrest, ventricular arrhythmia and pirouette-type tachycardia *torsade de pointes* (reported

predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see "Special warnings and precautions for use" and "Overdose" sections).
*Vascular disorders****:* rare – hypotension.
Respiratory system disorders: uncommon – shortness of breath (dyspnoea); not known – bronchospasm, allergic pneumonitis.
Gastrointestinal disorders: common – diarrhoea, vomiting, nausea; uncommon – abdominal pain, dyspepsia, flatulence, constipation; not known – haemorrhagic diarrhoea which may be indicative of enterocolitis, including pseudomembranous colitis (see "Special warnings and precautions for use" section), pancreatitis (see "Special warnings and precautions for use" section).
Hepatobiliary disorders: common – hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT); uncommon – blood bilirubin increased; not known – jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases (see "Special warnings and precautions for use" section), hepatitis.
*Skin and subcutaneous tissues disorders**:* uncommon – rash, pruritus, urticaria, hyperhidrosis; rare – drug reaction with eosinophilia and systemic symptoms (DRESS) (see "Special warnings and precautions for use" section), fixed drug eruption; not known – toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction (see "Special warnings and precautions for use" section), leukocytoclastic vasculitis; stomatitis, skin hyperpigmentation.
*Musculoskeletal system and connective tissue disorders***:* uncommon – arthralgia, myalgia; rare – tendon disorders (see "Contraindications" and "Special warnings and precautions for use" sections) including tendinitis (e.g. Achilles tendon); muscular weakness which may be of special importance in patients with myasthenia gravis (see "Special warnings and precautions for use" section); not known – rhabdomyolysis, tendon rupture (e.g. Achilles tendon; see "Special warnings and precautions for use" section), ligament rupture, muscle rupture, arthritis.
Renal and urinary disorders: uncommon – blood creatinine increased; rare – acute renal failure (e.g. due to interstitial nephritis).
*General disorders and administration site conditions***:* uncommon – asthenia; rare – pyrexia; not known – pain (including pain in the back, chest and extremities).
Other undesirable effects associated with fluoroquinolone administration: attacks of porphyria in patients with porphyria.

* Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.
** Mucocutaneous reactions may sometimes occur even after the first dose.
*** Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see "Special warnings and precautions for use" section).
**** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see "Special warnings and precautions for use" section).

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 3 years.

Storage conditions.
Store at the temperature not more than 25°C.
Keep out of reach of children.

Package.

5 or 10 tablets in a blister; 1 blister in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of its business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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