Professional Information for LEVOFLOXACIN 250 / 500 BIOTECH

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LEVOFLOXACIN 250 BIOTECH solution for infusion

LEVOFLOXACIN 500 BIOTECH solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEVOFLOXACIN 250 BIOTECH: Each 50 mL vial contains levofloxacin hemihydrate equivalent to 250 mg levofloxacin.

LEVOFLOXACIN 500 BIOTECH: Each 100 mL vial contains levofloxacin hemihydrate equivalent to 500 mg levofloxacin.

Sugar free.

Excipient with known effect:

LEVOFLOXACIN 250 BIOTECH contains 7,7 mmol (177 mg) sodium per 50 mL solution for infusion.

LEVOFLOXACIN 500 BIOTECH contains 15,4 mmol (354 mg) sodium per 100 mL solution for infusion.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Yellow to greenish yellow clear solution, practically free from particles. Solution is sterile with a pH of 4,1 to 5,1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LEVOFLOXACIN BIOTECH can be used in adults, in the treatment of the following bacterial infections:

Acute exacerbations of chronic bronchitis: caused by *H. influenzae, K. pneumoniae, S. aureus, M. catarrhalis, E. coli, H. parainfluenzae* or *S. pneumoniae*.

Community acquired pneumonia: caused by *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, Myocoplasma pneumoniae, Chlamydia pneumoniae* or Legionella pneumophlia.

Sinusitis: caused by *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis* or *H. parainfluenzae.*

Chronic bacterial prostatitis: due to *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis.*

Complicated urinary tract infections and acute pyelonephritis: caused by *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae* and *P. aeruginosa*.

Uncomplicated urinary tract infections in women: caused by *E. coli.*

Uncomplicated skin and soft tissue infections: caused by *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae* or *S. faecalis*.

Complicated skin and soft tissue infections: caused by *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*.

Intra-abdominal infections: caused by *E. coli* and anaerobic micro-organisms.

4.2 Posology and method of administration

LEVOFLOXACIN BIOTECH solution for infusion should be infused slowly over a period of not less than 30 minutes for a dosage of 250 mg, and not less than 60 minutes for a dosage of 500 mg. LEVOFLOXACIN BIOTECH solution for infusion should be used within three hours after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

It is usually possible to switch from initial intravenous treatment to the oral route after a few days, according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

LEVOFLOXACIN BIOTECH is administered once or twice daily.
The dosage depends on the type and severity of infection and sensitivity of the presumed causative pathogen. The duration of therapy varies according to the course of the disease. LEVOFLOXACIN BIOTECH 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.
The following daily dose are recommended for LEVOFLOXACIN BIOTECH:

Daily dosage recommended in patients with normal renal function:

Sinusitis due to *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis and H. parainfluenzae:* 500 mg once daily for 10 days.

Acute exacerbation of chronic bronchitis due to *H. influenzae, K. pneumoniae, S. aureus, M. catarrhalis, E. coli, H. parainfluenzae* and *S. pneumoniae*: 500 mg once daily for 5 - 10 days.

Community acquired pneumonia due to *H. influenzae, S. pneumoniae, S.* aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, *Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila:* 500 mg once or twice daily for 10 - 14 days.

(The higher dosage should be chosen in the presence of complicating factors e.g. co-morbidity, advanced age).

Chronic bacterial prostatitis due to *Eschericia coli, Enterrococcus faecalis, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis*: 500 mg once a day for 28 days.

Complicated urinary tract infections and acute pyelonephritis due to *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae, P. aeruginosa*: 250 mg once daily for 10 days.

Uncomplicated urinary tract infections in women due to *E. coli*: 250 mg once daily for 3 days.

Uncomplicated skin and skin structure infections due to *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E.coli, K. pneumoniae, S. faecalis*: 250 to 500 mg once daily for 7 - 10 days.

Complicated skin and skin structure infections due to *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*: 500 mg twice daily for 10 - 14 days.

Intra-abdominal infections due to *E. coli* and anaerobic micro-organisms: 500 mg once daily in combination with an antibiotic with anaerobic coverage for 10 -14 days.

Above indications when bacteraemia or septicaemia is present: 500 mg twice daily for 10 - 14 days.

Special populations

Daily dosage recommended in patients with impaired renal function:

Dosage must be adjusted in patients with impaired renal function according to the degree of impairment (creatinine clearance ≤ 50 mL/min):

Patients with a creatinine clearance between 20 and 50 mL/min:

Patients requiring 250 to 500 mg once daily: a single dose should be given initially and then reduced by half this dose once daily.

Patients requiring 500 mg twice daily: the initial dose should be 500 mg and then 250 mg should be given twelve hourly.

Patients with a creatinine clearance between 10 and 19 mL/min:

Patients requiring 250 mg once daily: a single dose should be given initially and then reduced to 125 mg every 48 hours.

Patients requiring 500 mg once daily: should be given a single dose initially and then this dose should be reduced to 125 mg every 24 hours.

Patients requiring 500 mg twice daily: should be given 500 mg initially and then this dose should be reduced to 125 mg every 12 hours.

Patients with creatinine clearance of less than 10 mL/min /min or in patients on haemodialysis or CAPD (continuous ambulatory peritoneal dialysis):

In patients where the prescribed dosage is 250 mg once daily: a single dose should be given initially and then this dose should be reduced to 125 mg every 48 hours.

Patients requiring 500 mg once daily: should be given a single dose initially and then this dose should be reduced to 125 mg every 24 hours.

Patients requiring 500 mg twice daily: should be given 500 mg initially and then this dose should be reduced to 125 mg every 24 hours.

Elderly patients or patients with hepatic impairment:

No adjustment of dosage is required in the elderly or in patients with impaired liver function.

4.3 Contraindications

The use of LEVOFLOXACIN BIOTECH is contraindicated in:

- Patients with hypersensitivity to levofloxacin, other quinolones, or any of the excipients listed in

section 6.1.

- Epilepsy.
- Patients with history of tendon disorders associated with fluoroquinolone administration.
- Children or adolescents (under 18 years of age) (see section 4.4).
- During pregnancy and lactation (see section 4.6).
- Patients with confirmed mitral valve and aortic valve regurgitation unless no safer appropriate alternative is available, has failed or is not well tolerated.
- Concomitant use of fluroquinolones with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

The use LEVOFLOXACIN BIOTECH should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with LEVOFLOXACIN BIOTECH should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

LEVOFLOXACIN BIOTECH should be used with caution in patients predisposed to seizures, such as patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar nonsteroidal anti-inflammatory drugs or with medicines which lower the cerebral seizure threshold, such as theophylline.

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before

initiating treatment and monitored during treatment with LEVOFLOXACIN BIOTECH or ACE inhibitors/angiotensin receptor blockers whether used separately and/or concomitantly.

There is some evidence, although inconclusive, of a possible association between oral fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and or aortic valve regurgitation (see section 4.3).

LEVOFLOXACIN BIOTECH should not be given to patients under 18 years of age.

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 BIOTECH 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.

Resistance:
Methicillin-resistant *Staphylococcus aureus* (MRSA) are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, LEVOFLOXACIN BIOTECH is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial medicines for the treatment of MRSA infections are considered inappropriate).

Resistance to fluoroquinolones of *E. coli* – the most common pathogen involved in urinary tract infections varies, prescribers are advised to take into account the local prevalence of resistance in *E. coli* to fluoroquinolones.

Infusion time:

The recommended infusion time of at least 30 minutes for LEVOFLOXACIN 250 BIOTECH and 60 minutes for LEVOFLOXACIN 500 BIOTECH should be observed. It is known for ofloxacin that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (l-isomer of ofloxacin) the infusion must be halted immediately.

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 1 000 mg levofloxacin and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided (see section 4.2).

At the first sign of tendinitis (e.g. painful swelling, inflammation) LEVOFLOXACIN BIOTECH 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 (see sections 4.3 and 4.8).

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 section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with LEVOFLOXACIN BIOTECH. If CDAD is suspected or confirmed, LEVOFLOXACIN BIOTECH should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicines 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 section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with active substances which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, (see section 4.8), treatment with levofloxacin should be discontinued.

Patients with G-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 medicines. 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 BIOTECH

should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions:

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their doctor, who will initiate appropriate emergency measures.

Severe bullous reactions:

Cases of severe bullous skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia:

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, 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 (see section 4.8).

Prevention of photosensitisation:

Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial ultraviolet (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 medicines are given concomitantly (see section 4.5).

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 section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if LEVOFLOXACIN BIOTECH is to be used in psychotic patients or in patients with history of psychiatric disease.

QT interval prolongation:

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

- Congenital long QT syndrome.
- Concomitant use of medicines that are known to prolong the QT interval (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia).
- 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 in these populations (see sections 4.2, 4.5, 4.8, and 4.9).

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 BIOTECH 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 section 4.8).

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 section 4.8). 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 BIOTECH 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 sections 4.7 and 4.8).

Superinfection:

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

Vascular disorders:

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. 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 in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a doctor in an emergency department (see section 4.8).

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.

Sodium content:

LEVOFLOXACIN 250 BIOTECH contains 7,7 mmol (177 mg) sodium per 50 mL solution for infusion.

LEVOFLOXACIN 500 BIOTECH contains 15,4 mmol (354 mg) sodium per 100 mL solution for infusion.

To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on LEVOFLOXACIN BIOTECH

Theophylline, fenbufen or similar nonsteroidal 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, nonsteroidal anti-inflammatory drugs, or other medicines 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 medicines 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 medicines that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

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 medicines: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of LEVOFLOXACIN BIOTECH on other medicines

Ciclosporin:

The half-life of ciclosporin was increased by 33 % when coadministered 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 section 4.4).

Medicines known to prolong QT interval:

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving medicines known to prolong the QT interval (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4 – QT interval prolongation).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

In the absence of human data and since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism levofloxacin is contraindicated in, and must not be used during pregnancy (see section 4.3).

Breastfeeding

Levofloxacin is contraindicated in breastfeeding women. There is insufficient evidence on the excretion of levofloxacin in human milk, however other fluoroquinolones are excreted in human breast milk. (see section 4.3).

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on 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).

4.8 Undesirable effects

System organ class	Frequent	Less frequent	Not known (cannot be estimated from available data)

Infections and infestations		Fungal infection including Candida infection Pathogen resistance	
Blood and lymphatic system disorders		Thrombocytopenia Neutropenia Leukopenia Eosinophilia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders		Angioedema Hypersensitivity (see section 4.4)	Anaphylactic[a] shock and anaphylactoid[a] shock (see section 4.4)
Metabolism and nutrition disorders		Anorexia Hypoglycaemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders*	Insomnia	Anxiety Confusional state Nervousness Psychotic reactions (with hallucination, paranoia) Depression	Psychotic disorder with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)

		Agitation Abnormal dreams Nightmares	
Nervous system disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia Convulsion (see sections 4.3 and 4.4) Paraesthesia	Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders*		Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4)
Ear and labyrinth disorders*		Vertigo Tinnitus	Hearing loss Hearing impaired
Cardiac disorders		Tachycardia	Ventricular tachycardia,

		Palpitation	which may result in cardiac arrest. Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9)
Vascular disorders	Phlebitis	Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm Pneumonitis allergic
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation	Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis
Hepato-biliary disorders	Hepatic enzyme increased (ALT/AST,	Blood bilirubin increased	Jaundice and severe liver injury, including

	alkaline phosphatase, GGT)		fatal cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash Pruritus Urticaria Hyperhidrosis	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon, Muscular weakness which may be of special	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis

		importance in patients with myasthenia gravis (see section 4.4))	
Renal and urinary disorders		Blood creatinine increased Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions*	Infusion site reaction (pain, reddening)	Asthenia Pyrexia	Pain (including pain in back, chest, and extremities)

* 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 tendinitis, 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 section 4.4).

[a]Anaphylactic and anaphylactoid reactions may sometimes occur, even after the first dose.

[b]Mucocutaneous reactions may sometimes occur even after the first dose.

Other undesirable effects which have been associated with fluoroquinolone administration include:

- Attacks of porphyria in patients with porphyria.

Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation was diagnosed.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of LEVOFLOXACIN BIOTECH is important. It allows continued monitoring of the benefit/risk balance of LEVOFLOXACIN BIOTECH. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The most important signs to be expected following acute overdose of levofloxacin are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

Gastrointestinal reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Quinolone antibacterials – fluoroquinolones.

ATC code: J01MA12.

Levofloxacin is a synthetic broad-spectrum antibacterial fluoroquinolone and is the S (-) enantiomer of the racemic drug substance ofloxacin.

Mechanism of action:

As a fluoroquinolone antibacterial medicine, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV. Levofloxacin is bactericidal *in vitro*. Its antibacterial spectrum covers many Gram-positive and Gram-negative bacteria.

PK/PD relationship:

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 medicines.

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

[#] Methicilin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones,

including levofloxacin.

5.2 Pharmacokinetic properties

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 - 2 h. The absolute bioavailability is 99 to 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.

Multiple doses of 500 mg once daily with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within three days.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bone tissue, bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebro-spinal 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 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 ($t_{½}$: 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 1 000 mg.

Patients with renal insufficiency:

The pharmacokinetics of levofloxacin is affected by renal impairment. With decreasing renal function renal elimination (Cl_{cr}) and clearance (Cl_R) are decreased, and elimination half-lives ($t_{1/2}$) increased as shown in the table below:

Cl_{cr} (mL/min)	< 20	20 - 40	50 - 80
Cl_R (mL/min)	13	26	57
($t_{1/2}$) (h)	35	27	9

Elderly patients:

There are no significant differences in levofloxacin pharmacokinetics between young and elderly patients, except those associated with differences in creatinine clearance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Edetate disodium

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections.

6.2 Incompatibilities

LEVOFLOXACIN BIOTECH solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate). LEVOFLOXACIN BIOTECH must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Before opening:

24 months.

Once opened:

Use immediately.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the outer carton to protect from light.

Do not freeze.

6.5 Nature and contents of container

LEVOFLOXACIN 250 BIOTECH is packed in 50 mL colourless glass vial with grey chlorobutyl

rubber stopper and aluminium cap with polypropylene flip off seal and into a cardboard carton.

LEVOFLOXACIN 500 BIOTECH is packed in 100 mL colourless glass vial with grey chlorobutyl rubber stopper and aluminium cap with polypropylene flip off seal and into a cardboard carton.

6.6 Special precautions for disposal and other handling

This product is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

LEVOFLOXACIN BIOTECH is compatible with the following infusion solutions:

- 0,9 % sodium chloride solution.
- 5 % dextrose injection.
- 2,5 % dextrose in Ringer's solution.
- Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

See section 6.2 for incompatibilities.

The solution should be visually inspected prior to use. It must only be used if the solution is a clear and greenish yellow coloured solution, practically free from particles.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBERS

LEVOFLOXACIN 250 BIOTECH: 43/20.1.1/0231

LEVOFLOXACIN 500 BIOTECH: 43/20.1.1/0232

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 April 2014

10. DATE OF REVISION OF THE TEXT

06 March 2023