**Professional Information (PI)**

**SCHEDULING STATUS: S4**

## 1. NAME OF THE MEDICINE

**LEVOFLOXACIN 5 mg/mL (100 mL) FRESENIUS** solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL solution for infusion contains levofloxacin hemihydrate equivalent to 5 mg levofloxacin.

Sugar free.

Excipients with known effect:

LEVOFLOXACIN 5 mg/mL (100 mL) FRESENIUS contains 3,54 mg of sodium per mL.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for infusion.

Yellow to greenish yellow clear solution free from visible particles.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

LEVOFLOXACIN FRESENIUS is indicated in adults for the treatment of the following bacterial infections when the oral route is not suitable.

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

- **Pneumonia (community acquired):** caused by *H. influenzae,* methicillin-sensitive *S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, Mycoplasma pneumoniae, Chlamydia pneumoniae* or *Legionella pneumophila.*
- **Sinusitis:** caused by *H. influenzae, S. aureus, M. catarrhalis* or *H. parainfluenzae*.
- **Urinary tract infections (complicated) and acute pyelonephritis:** caused *by E. coli, S. faecalis, P. mirabilis, Enterobacter cloacae* and *P. aeruginosa*.
- **Uncomplicated urinary tract infections in women:** caused by *E. coli, K. pneumoniae*.
- **Skin and soft tissue infections (uncomplicated):** caused by methicillin-sensitive *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae* or *S. faecalis*.
- **Skin and soft tissue infections (complicated):** caused by methicillin-sensitive *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae* or *K. oxytoca*.
- **Intra-abdominal infections:** caused by *E. coli* and anaerobic micro-organisms.

In the treatment of infections caused by *P. aeruginosa*, an aminoglycoside should be administered concomitantly.

## 4.2 Posology and method of administration

***Posology***

**The following daily dose is recommended for LEVOFLOXACIN FRESENIUS:**

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.

***Daily dosage recommended in patients with normal renal function:***

**Bronchitis, bacterial exacerbations:** 500 mg once daily for 5 – 10 days.

**Pneumonia, community acquired:** 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).

**Sinusitis:** 500 mg once daily for 10 – 14 days.

**Urinary tract infections (uncomplicated) in women:** 250 mg once daily for 3 days.

**Uncomplicated skin and soft tissue infections:** 500 mg once daily for 10 – 14 days.

**Intra-abdominal infections:** 500 mg once daily in combination with an antibiotic with anaerobic coverage for 10 – 14 days.

Above infections, 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:*

250 or 500 mg once daily: A normal single dose should be given initially and then reduced by half this dose once daily.

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:*

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

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

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

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

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

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

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

***Impaired liver function***

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

***Elderly population***

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function (see also section 4.4 "**Tendinitis and tendon rupture**" and "**QT interval prolongation**").

***Paediatric population***

LEVOFLOXACIN FRESENIUS is contraindicated in children and growing adolescents under 18 years of age (see section 4.3).

***Method of administration***

Intravenous infusion.

LEVOFLOXACIN FRESENIUS 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.
For incompatibilities see section 6.2 and for compatibility with other infusion solutions see section 6.6.

## 4.3 Contraindications

- Previous hypersensitivity reaction to levofloxacin, other quinolones, or to any other of the ingredients of LEVOFLOXACIN FRESENIUS (see section 6.1).
- Epilepsy.
- Patients with history of tendon disorders associated with fluoroquinolone administration.
- Children or growing adolescents (under 18 years of age).
- Pregnancy and lactation (see section 4.6).
- Patients with mitral valve and/or aortic valve regurgitation unless no safer appropriate antibiotic is available, has failed or is not well tolererated.

## 4.4 Special warnings and precautions for use

The use of LEVOFLOXACIN FRESENIUS 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 FRESENIUS should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

**Prolonged, disabling and potentially irreversible serious adverse drug reactions**

Less frequent 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 FRESENIUS should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their doctor for advice.

**Risks of resistance**

Methicillin-resistant *S. aureus* is very likely to possess co-resistance to fluoroquinolones, including LEVOFLOXACIN FRESENIUS. Therefore, LEVOFLOXACIN FRESENIUS is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to LEVOFLOXACIN FRESENIUS (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 across regions. Doctors are advised to take into account the local prevalence of resistance in *E. coli* to LEVOFLOXACIN FRESENIUS.

**Infusion Time**

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg LEVOFLOXACIN FRESENIUS should be observed (see section 4.2). It is known for ofloxacin, that during infusion tachycardia and a temporary decrease in blood pressure may develop. Less frequently, 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 FRESENIUS, (*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, patients receiving daily doses of 1000 mg, 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 FRESENIUS 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.

***Clostridium difficile*-associated disease**

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with LEVOFLOXACIN FRESENIUS (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 FRESENIUS. If CDAD is suspected or confirmed, LEVOFLOXACIN FRESENIUS 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 FRESENIUS 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 prone to seizures, such as patients with pre-existing central nervous system disorders, or concomitant treatment with medicines that lower the cerebral seizure threshold, such as non-steroidal anti-inflammatory medicines (NSAIDs) or theophylline (see section 4.5). In case of convulsive seizures (see section 4.8), treatment with LEVOFLOXACIN FRESENIUS 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 FRESENIUS has to be used in these patients, potential occurrence of haemolysis should be monitored.

**Patients with renal impairment**

Since LEVOFLOXACIN FRESENIUS is excreted mainly by the kidneys, the dose of LEVOFLOXACIN FRESENIUS should be adjusted in patients with renal impairment (see section 4.2).

**Hypersensitivity reactions**

LEVOFLOXACIN FRESENIUS 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 or an emergency doctor, 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 FRESENIUS (see section 4.8). 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 FRESENIUS 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 FRESENIUS, treatment with LEVOFLOXACIN FRESENIUS 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, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In patients with diabetes mellitus, careful monitoring of blood glucose is recommended (see section 4.8).

**Prevention of photosensitisation**

Photosensitisation has been reported with LEVOFLOXACIN FRESENIUS (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong

sunlight or longer wavelength ultraviolet (UVA) rays from sun beds 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 FRESENIUS 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 FRESENIUS. Less frequently these have progressed to suicidal thoughts and self-endangering behaviour - sometimes after only a single dose of LEVOFLOXACIN FRESENIUS (see section 4.8). In the event that the patient develops these reactions, LEVOFLOXACIN FRESENIUS should be discontinued and appropriate measures instituted.

Caution is recommended if LEVOFLOXACIN FRESENIUS 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 FRESENIUS, 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 medicines. Therefore, caution should be taken when using fluoroquinolones, including LEVOFLOXACIN FRESENIUS, in these populations. (See sections 4.2 "***Elderly population***", 4.5, 4.8 and 4.9).

**Porphyria**

Fluoroquinolones, such as LEVOFLOXACIN FRESENIUS, have been known to trigger porphyria attacks in patients with porphyria.

**Peripheral neuropathy**

Cases of sensory or sensorimotor polyneuropathy, which can be rapid in its onset and resulting in paraesthesia, hypoesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients being treated with LEVOFLOXACIN FRESENIUS 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 a potentially irreversible condition (see section 4.8).

**Hepatobiliary disorders**

Cases of hepatic necrosis up to life threatening hepatic failure have been reported with LEVOFLOXACIN FRESENIUS, 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 a tender abdomen.

**Exacerbation of myasthenia gravis**

Fluoroquinolones, including LEVOFLOXACIN FRESENIUS, 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 FRESENIUS 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).

**Superinfections**

Superinfections with *Streptococcus pneumoniae* have been reported. The use of LEVOFLOXACIN FRESENIUS, 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 FRESENIUS, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by a more specific method.

LEVOFLOXACIN FRESENIUS 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. 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 section 4.8).
A thorough cardiovascular examination including an echocardiogram, should be performed before fluoroquinolones are prescribed. LEVOFLOXACIN FRESENIUS should not be prescribed to patients with mitral valve and or aortic valve regurgitation (see section 4.3).
Consider other therapeutic options in patients with a positive family history or who have been diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in the 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, Behçet´s disease, hypertension, rheumatoid arthritis) or additionally

- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- 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 doctor 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 section 4.8).

**Blood disorders**

Bone marrow failure including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia, or agranulocytosis may develop during treatment with levofloxacin (see section 4.8). If any of these blood disorders are suspected, blood counts

should be monitored. In case of abnormal results, discontinuation of treatment with levofloxacin should be considered.

**Myoclonus**

Cases of myoclonus have been reported in patients receiving levofloxacin (see section 4.8). The risk of myoclonus is increased in older patients, and in patients with renal impairment if the dose of levofloxacin is not adjusted as per the creatinine clearance. Levofloxacin should be discontinued immediately at the first occurrence of myoclonus and appropriate treatment should be initiated.

**Sodium content**

LEVOFLOXACIN FRESENIUS contains 3,54 mg sodium per 1 mL, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicines and other forms of interaction

**Effect of other medicines on LEVOFLOXACIN FRESENIUS**

***Theophylline, fenbufen or similar non-steroidal anti-inflammatory medicines***

No pharmacokinetic interactions of LEVOFLOXACIN FRESENIUS were found with theophylline in a clinical study. However, LEVOFLOXACIN FRESENIUS is known to inhibit hepatic metabolism of some medicines and may interfere with the clearance of medicines, such as theophylline, or non-steroidal anti-inflammatory medicines that lower the seizure threshold.

LEVOFLOXACIN FRESENIUS concentrations were about 13 % higher in the presence of fenbufen than when administered alone.

***Probenecid and cimetidine***

Caution should be exercised when LEVOFLOXACIN FRESENIUS is co-administered with medicines that affect 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 FRESENIUS were not affected to any clinically relevant extent when LEVOFLOXACIN FRESENIUS was administered together with the following medicines: calcium carbonate, digoxin, glibenclamide, ranitidine.

**Effect of LEVOFLOXACIN FRESENIUS on other medicines**

***Ciclosporin***

The half-life of ciclosporin was increased by 33 % when co-administered with LEVOFLOXACIN FRESENIUS.

***Vitamin K antagonists***

Increased coagulation tests (PT/INR) and/or bleeding which may be severe, has been reported in patients treated with LEVOFLOXACIN FRESENIUS in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests should be monitored in patients treated with vitamin K antagonists.

***Medicines known to prolong QT interval***

LEVOFLOXACIN FRESENIUS 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 FRESENIUS did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that LEVOFLOXACIN FRESENIUS is not a CYP1A2 inhibitor.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy and lactation**

LEVOFLOXACIN FRESENIUS is contraindicated during pregnancy and lactation (see section 4.3).

Animal studies have shown that joint development in growing organisms has been adversely affected.

**Fertility**

LEVOFLOXACIN FRESENIUS caused no impairment of fertility or reproductive performance in rats.

## 4.7 Effects on ability to drive and use machines

LEVOFLOXACIN FRESENIUS may cause drowsiness, dizziness/vertigo or visual disturbances (see section 4.8) and may impair the patient’s ability to concentrate and react. Caution is advised when driving or operating machinery.

## 4.8 Undesirable effects

*a) Summary of the safety profile*

Allergic manifestations may occur, in particular hypersensitivity reactions of the skin such as pruritus, rash, urticaria and vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioedema, hypotension and anaphylactic-like shock.

*b) Tabulated list of adverse reactions*

| **System organ class** | **Frequent** | **Less frequent** | **Frequency unknown** (cannot be estimated from the available data) |
|---|---|---|---|
| **Infections and infestations** | | Fungal infection including Candida infection<br>Vaginal candidiasis<br>Fungal overgrowth<br>Pathogen resistance<br>Proliferation of other resistant micro-organisms | |
| **Blood and the lymphatic system disorders** | | Leukopenia<br>Eosinophilia<br>Neutropenia<br>Thrombocytopenia | Bone marrow failure including aplastic anaemia<br>Pancytopenia<br>Agranulocytosis<br>Haemolytic anaemia |

| | | | |
|---|---|---|---|
| **Immune system disorders** | | Hypersensitivity<br>Angioedema | Anaphylactic shock[a]<br>Anaphylactoid shock[a] |
| **Endocrine disorders** | | Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) | |
| **Metabolism and nutrition disorders** | | Anorexia<br>Hypoglycaemia<br>Hypoglycaemic coma | Hyperglycaemia |
| **Psychiatric disorders** | Sleep disturbances<br>Insomnia | Encephalopathy<br>Confusion<br>Coma<br>Anxiety<br>Nervousness<br>Psychotic reactions (with e.g. hallucinations, paranoia)<br>Restlessness<br>Agitation<br>Depression<br>Abnormal dreams<br>Nightmares | Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt<br>Mania |
| **Nervous system disorders** | Headache<br>Dizziness | Unsteady gait<br>Somnolence<br>Tremor<br>Dysgeusia<br>Convulsions | Peripheral sensory neuropathy<br>Peripheral sensory motor neuropathy |

| | | | |
|---|---|---|---|
| | | Paraesthesia | Parosmia including anosmia<br>Dyskinesia<br>Extrapyramidal disorder<br>Ageusia<br>Syncope<br>Benign intracranial hypertension<br>Myoclonus |
| **Eye disorders** | | Visual disturbances<br>Blurred vision | Transient vision loss |
| **Ear and labyrinth disorders** | | Vertigo<br>Tinnitus | Hearing loss<br>Hearing impaired |
| **Cardiac disorders** | | Tachycardia<br>Palpitation | Ventricular tachycardia, which may result in cardiac arrest<br>Ventricular arrhythmia and *torsade de pointes*[b]<br>QT prolongation |
| **Vascular disorders** | Phlebitis | Hypotension<br>Oedema<br>Hot flushes | |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | Dyspnoea | Bronchospasm<br>Allergic pneumonitis |
| **Gastrointestinal disorders** | Diarrhoea<br>Vomiting<br>Nausea<br>Abdominal and stomach cramps | Abdominal pain<br>Dyspepsia<br>Flatulence<br>Constipation | Haemorrhagic diarrhoea<br>Enterocolitis<br>Pseudomembranous colitis<br>Pancreatitis (see section 4.4) |
| **Hepatobiliary disorders** | Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT) | Blood bilirubin increased | Jaundice<br>Severe liver injury<br>Acute liver failure<br>Hepatitis |
| **Skin and subcutaneous tissue disorders**[c] | | Hypersensitivity reactions of the skin<br>Rash<br>Pruritus<br>Urticaria<br>Hyperhidrosis<br>Sweating<br>Drug Reaction with Eosinophilia and | Toxic epidermal necrolysis<br>Stevens-Johnson syndrome<br>Erythema multiforme<br>Photosensitivity reactions<br>Leukocytoclastic vasculitis<br>Stomatitis |

| | | | |
|---|---|---|---|
| | | Systemic Symptoms (DRESS)<br>Fixed drug eruption<br>Hypersensitivity vasculitis | Skin hyperpigmentation |
| **Musculoskeletal and connective tissue disorders** | | Arthralgia<br>Myalgia<br>Tendon disorders including tendinitis (e.g. Achilles tendon)<br>Muscular weakness | Rhabdomyolysis<br>Tendon rupture (e.g. Achilles tendon)<br>Ligament rupture<br>Muscle rupture<br>Arthritis |
| **Renal and urinary disorders** | | Blood creatinine increased<br>Acute renal failure<br>Interstitial nephritis<br>Crystalluria<br>Transient increase in blood urea | |
| **Reproductive system and breast disorders** | | Gynaecomastia | |
| **General disorders and administrative site conditions** | Infusion site reaction (pain, reddening) | Asthenia<br>Pyrexia | Pain (including pain in back, chest, and extremities) |

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

[b] Reported predominantly in patients with risk factors of QT prolongation.

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

*c) Description of selected adverse reactions*

Jaundice and severe liver injury, including fatal cases with acute liver failure, have been reported with LEVOFLOXACIN FRESENIUS, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.4).

Less frequently cases of prolonged (up to months or years), disabling and potentially irreversible serious adverse 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).

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 section 4.4). Due to insufficient post-marketing information in the reported cases, it is unknown whether fluroquinolone use was the causative factor, or a contributory factor or played no role in the preported cases where mitral cases and/or aortic regurgitation was diagnosed.

Other undesirable effects related to the class of fluoroquinolones include extrapyramidal symptoms and other disorders of muscular coordination, hypersensitivity vasculitis and attacks of porphyria in patients with porphyria (see section 4.4).

*d) Paediatric population*

LEVOFLOXACIN FRESENIUS is contraindicated in children and growing adolescents under 18 years of age (see section 4.3).

*e) Other special populations*

The risk of tendon rupture (Achilles tendon) is higher in the elderly. Elderly patients and women may be more sensitive to QTc-prolonging medicines. Therefore, caution should be taken when using fluoroquinolones, including LEVOFLOXACIN FRESENIUS, in these populations. (See sections 4.2 "***Elderly population***", 4.5, 4.8 and 4.9).

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

## 4.9 Overdose

**Symptoms**

The symptoms that can be expected from an acute overdosage of LEVOFLOXACIN FRESENIUS are central nervous system symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures.

CNS effects including confusion, convulsions, myoclonus, hallucinations and tremor have been observed in post-marketing experience.

Gastrointestinal reactions such as nausea and mucosal erosions.

In clinical pharmacology studies performed with a supra-therapeutic dose, increase in QT interval has been seen.

**Treatment**

Treatment of overdose is symptomatic and supportive.

In the event of overdose the patient should be carefully observed (including ECG monitoring) and symptomatic treatment should be implemented.

LEVOFLOXACIN FRESENIUS is not effectively removed by haemodialysis, including peritoneal dialysis and CAPD. 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 broad-spectrum bactericidal medicine from the chemical group fluoroquinolone. Levofloxacin is the pure S (-) enantiomer of ofloxacin.

**Mechanism of action:**

The bactericidal action of levofloxacin results from interference with the enzymes topoisomerase IV and DNA gyrase, which are needed for the DNA replication, transcription, repair and recombination.

Levofloxacin is bactericidal *in vitro*. Cross-resistance exists between levofloxacin and other fluoroquinolones *in vitro*.

The antibacterial spectrum of levofloxacin covers many Gram-positive and Gram-negative bacteria.

**Resistant organisms**: *C.jejuni, Salmonella, N. gonorrhoeae* and *S. pneumoniae*.

### 5.2 Pharmacokinetic properties

***Distribution, metabolism and excretion:***

Levofloxacin is approximately 30-40 % bound to serum protein. Steady-state is achieved within three days.

Levofloxacin is metabolised to a small degree to inactive metabolites being desmethyl levofloxacin and levofloxacin-*N*-oxide. The elimination half-life of levofloxacin is six to eight hours after intravenous administration. Levofloxacin is excreted largely unchanged, primarily via the kidney.

***Distribution in tissues and fluids:***

Levofloxacin penetrates well into lung tissue, bone tissue, bronchial mucosa, epithelial lining fluid and blister fluid.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride

Sodium hydroxide (1 M) (for pH-adjustment)

Hydrochloric acid 37 % (for pH-adjustment)

Water for injection.

### 6.2 Incompatibilities

LEVOFLOXACIN FRESENIUS should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).

If its compatibility with other infusion solutions has not been proven, LEVOFLOXACIN FRESENIUS should as a rule be administered separately.
LEVOFLOXACIN FRESENIUS must not be mixed with other medicines except those mentioned in section 6.6.

## 6.3 Shelf life

Unopened:

LDPE bottlepack: 36 months

Freeflex (polyolefine) bags: 24 months

In-use: Use within 3 hours after perforation of the rubber stopper (see section 6.6).

For the diluted product chemical and physical stability has been demonstrated for 3 hours at or below 25 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 3 hours at or below 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep in outer container until required for use.

Do not refrigerate or freeze.

For storage after opening or dilution, see section 6.3.

## 6.5 Nature and contents of container

100 mL solution in clear, opaque LDPE bottlepack containers with one or two rubber discs inside a LDPE, HDPE or polypropylene cap tightly welded with a flange.

Packed in 1, 20 or 25 x 100 mL.

100 mL solution in overwrapped freeflex (polyolefine) bags.

Packed in 10 x 100 mL.

Not all container closure systems may be marketed.

### 6.6 Special precautions for disposal and other handling

LEVOFLOXACIN FRESENIUS should be used within 3 hours after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

For single use. Discard unused portion.

LEVOFLOXACIN FRESENIUS is compatible with the following infusion solutions (may be stored for up to 3 hours at 25 °C when diluted to a concentration of 0,5 mg/mL or 2,0 mg/mL levofloxacin):

0,9 % sodium chloride (saline)

5 % dextrose/glucose

2,5 % dextrose/glucose in Ringer solution.

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

See section 6.2 for incompatibilities.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7, Midrand, 1685

South Africa

Telephone number: +27 (0)11 545 0000

## 8. REGISTRATION NUMBER

45/20.1.1/0139

## 9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

05 June 2014

## 10. DATE OF REVISION OF THE TEXT

13 January 2026