

## CORE SAFETY PROFILE

### LEVOFLOXACIN

**Formulations:** 250 and 500 mg film-coated tablets  
5 mg/ml solution for infusion

#### 4.3 Contraindications

<Productname> must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or any of the excipients,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents,
- during pregnancy,
- in breast-feeding women.

#### 4.4 Special warnings and precautions for use

In the most severe cases of pneumococcal pneumonia <Productname> may not be the optimal therapy.

Nosocomial infections due to *P. aeruginosa* may require combination therapy.

Methicillin-resistant *S. aureus* are 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.

Applies to iv form only:

##### *Infusion Time*

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg <Productname> solution for infusion 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.

##### *Sodium content*

This medicinal product contains 154 mmol/l (3.54 g/l) of sodium. To be taken into consideration by patients on a controlled sodium diet.

Applies to film-coated tablet and iv forms:

##### *Tendinitis and tendon rupture*

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed <Productname>. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment

with <Productname> must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. (See section 4.3 and 4.8)

#### *Clostridium difficile-associated disease*

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with <Productname> (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 <Product name>. If CDAD is suspected or confirmed, <Productname> 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. <Productname> 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 drugs that 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 agents, and so levofloxacin should be used with caution.

#### *Patients with renal impairment*

Since levofloxacin is excreted mainly by the kidneys, the dose of <Productname> 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 physician or an emergency physician, who will initiate appropriate emergency measures.

#### *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. In these 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 UV rays (e.g. sunray lamp, solarium), 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 <Productname> in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs 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 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, 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. hypokalemia, hypomagnesemia)
  - elderly
  - cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- (See section 4.2 *Elderly*, section 4.5, section 4.8, section 4.9).

#### *Peripheral neuropathy*

Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset (see section 4.8). Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

#### *Opiates*

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.

#### *Hepatobiliary disorders*

Cases of hepatic necrosis up to life threatening 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*

Levofloxacin should be used with caution in patients with a history of myasthenia gravis (see section 4.8).

#### *Superinfection*

As with other antibiotics, the use of levofloxacin, especially if prolonged, may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

### **4.5 Interactions with other medicinal products and other forms of interaction**

#### Effect of other medicinal products on <Productname>

Applies to film-coated tablets form only:

*Iron salts, magnesium- or aluminium-containing antacids*

Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids are administered concomitantly with <Productname> tablets. It is recommended that preparations containing divalent or trivalent cations such as iron salts, or magnesium- or aluminium-containing antacids should not be taken 2 hours before or after <Productname> tablet administration (see section 4.2). No interaction was found with calcium carbonate.

*Sucralfate*

The bioavailability of <Productname> tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and <Productname>, it is best to administer sucralfate 2 hours after the <Productname> tablet administration (see section 4.2).

Applies to film-coated tablet and iv forms:

*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 coadministered with drugs 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 were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of <Productname> on other medicinal products

Applies to film-coated tablet and iv forms:

*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).

*Drugs known to prolong QT interval*

Version 1.0

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, 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.

#### Other forms of interactions

##### *Applies to film-coated tablet forms only:*

#### *Food*

There is no clinically relevant interaction with food. <Productname> tablets may therefore be administered regardless of food intake.

### **4.6 Pregnancy and lactation**

#### *Pregnancy*

Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, <Productname> must not be used in pregnant women (see section 4.3).

#### *Lactation*

In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weightbearing cartilage of the growing organism, <Productname> must not be used in breast-feeding women (see section 4.3).

### **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**

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

Frequencies are defined using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10000$ ,  $< 1/1000$ ), 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.

System organ class	Common ( $\geq 1/100$ to $< 1/10$ )	Uncommon ( $\geq 1/1,000$ to $< 1/100$ )	Rare ( $\geq 1/10,000$ to $< 1/1,000$ )	Very rare ( $< 1/10,000$ )	Not known (cannot be estimated from available data)
Infections and infestations		Fungal infection Pathogen resistance			

<b>System organ class</b>	<b>Common (≥1/100 to &lt;1/10 )</b>	<b>Uncommon (≥1/1,000 to &lt;1/100)</b>	<b>Rare (≥1/10,000 to &lt;1/1,000)</b>	<b>Very rare (&lt;1/10,000)</b>	<b>Not known (cannot be estimated from available data)</b>
Blood and the Lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia		Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)		Anaphylactic shock <sup>a</sup> Anaphylactoid shock <sup>a</sup> (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)		Hyperglycaemia (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares		Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion (see section 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
Eye disorders			Visual disturbances such as blurred vision		Transient vision loss
Ear and Labyrinth disorders		Vertigo	Tinnitus		Hearing lossHearing impaired
Cardiac disorders			Tachycardia		Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), electrocardiogram

System organ class	Common (≥1/100 to <1/10 )	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)
					QT prolonged (see section 4.4 and section 4.9)
Vascular disorders	<i>Applies to iv form only:</i> 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
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased			Jaundice and severe liver injury, including cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders <sup>b</sup>		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 section 4.3 and 4.4) including tendonitis (e.g. Achilles tendon) Muscular weakness which may be of special		Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see section 4.3 and 4.4) Muscle rupture Arthritis

Version 1.0

System organ class	Common (≥1/100 to <1/10 )	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known (cannot be estimated from available data)
			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	<i>Applies to iv form only:</i> Infusion site reaction (pain, reddening)	Asthenia	Pyrexia		Pain (including pain in back, chest, and extremities)

<sup>a</sup> Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.

<sup>b</sup> 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.

## 4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of <Productname> are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.

*Applies to film-coated tablets only:* Gastro-intestinal reactions such as nausea and mucosal erosions.

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

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.

*Applies to film-coated tablets only:* Antacids may be used for protection of the gastric mucosa.