1. NAME OF THE MEDICINAL PRODUCT

Tavanic® 5 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

50 ml solution for infusion contains 250 mg levofloxacin as levofloxacin hemihydrate.
100 ml solution for infusion contains 500 mg levofloxacin as levofloxacin hemihydrate.

Excipients with known effect:
50 ml solution for infusion contains 7.9 mmol (181 mg) sodium.
100 ml solution for infusion contains 15.8 mmol (363 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, greenish-yellow, isotonic solution with a pH value of 4.3 – 5.3 and an osmolarity of 282 – 322 mOsm/l.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tavanic solution for infusion is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- community-acquired pneumonia,
- complicated skin and soft-tissue infections.

For the above-mentioned infections, Tavanic should be used only when antibiotics usually recommended for the initial treatment of these infections are not considered to be indicated.

- pyelonephritis and complicated urinary tract infections,
- chronic bacterial prostatitis,
- inhalation anthrax: for post-exposure prophylaxis and as curative treatment (see section 4.4).

Consideration should be given to the official recommendations on the appropriate use of antibiotics.

4.2 Posology and method of administration

Tavanic solution for infusion is slowly infused once or twice daily via the intravenous route. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.
Treatment with Tavanic may, following the initial intravenous therapy, be switched to an oral formulation according to the SPC for the film-coated tablets and depending on the patient's condition. Given the bioequivalence of the parenteral and oral forms, the same dose can be used.

Posology
For Tavanic, the following dosage recommendations can be given:

See table above

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

Indication	Daily dosage (according to severity)	Duration of treatment[1] (according to severity)
Community-acquired pneumonia	500 mg once or twice daily	7 – 14 days
Pyelonephritis	500 mg once daily	7 – 10 days
Complicated urinary tract infections	500 mg once daily	7 – 14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated skin and soft tissue infections	500 mg once or twice daily	7 – 14 days
Inhalation anthrax	500 mg once daily	8 weeks

[1] The duration of treatment includes both intravenous and oral therapy. The time to switch from intravenous to oral administration depends on the patient's condition, but is normally 2 to 4 days after the start of treatment.

Special patient groups
See table below

Impaired liver function
No dose adjustment is required, as levofloxacin is not metabolised to any relevant extent in the liver and is mainly excreted by the kidneys.

Elderly patients
Apart from taking renal function into consideration, no further dose adjustment is required in elderly patients (see section 4.4 "Tendinitis and tendon rupture" and "QT interval prolongation").

Paediatric population
Tavanic is contraindicated in children and growing adolescents (see section 4.3).

Method of administration
Tavanic solution for infusion is intended only for slow intravenous infusion and is administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg levofloxacin and at least 60 minutes for 500 mg levofloxacin (see also section 4.4).

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

4.3 Contraindications

Levofloxacin solution for infusion must not be used:

- in patients with hypersensitivity to levofloxacin or other quinolones, or to any of the excipients listed in section 6.1,
- in patients with epilepsy,
- in patients with a known history of tendon disorders after previous fluoroquinolone use,
- in children and growing adolescents,
- during pregnancy,
- in breast-feeding women.

4.4 Special warnings and precautions for use

Methicillin-resistant *S. aureus* are likely to possess co-resistance to fluoroquinolones (including levofloxacin). In known or suspected MRSA infections, levofloxacin is therefore not recommended for treatment, unless laboratory results confirm susceptibility of the pathogen to levofloxacin (and commonly recommended antibiotics for the treatment of MRSA are not considered to be indicated).

Resistance of *E. coli* – the most common pathogen in urinary tract infections – to fluoroquinolones varies within the European Union. When prescribing, physicians should consider the local prevalence of resistance in *E. coli* to fluoroquinolones.

Inhalation anthrax: Use in humans is based on *in vitro Bacillus anthracis* susceptibility data and on experimental data in animals together with limited human data.

Impaired renal function (creatinine clearance ≤ 50 ml/min)

	Dosage regimen		
	250 mg/24 hours	**500 mg/24 hours**	**500 mg/12 hours**
Creatinine clearance	First dose: 250 mg	First dose: 500 mg	First dose: 500 mg
50 – 20 ml/min	then: 125 mg/24 hours	then: 250 mg/24 hours	then: 250 mg/12 hours
19 – 10 ml/min	then: 125 mg/48 hours	then: 125 mg/24 hours	then: 125 mg/12 hours
<10 ml/min (including haemodialysis and CAPD)[1]	then: 125 mg/48 hours	then: 125 mg/24 hours	then: 125 mg/24 hours

[1] No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Treating physicians should refer to national or international consensus papers when treating anthrax.

Infusion time

The recommended infusion time of at least 30 minutes for 250 mg levofloxacin or at least 60 minutes for 500 mg levofloxacin should be observed. It is known for ofloxacin that, during infusion, tachycardia and a temporary decrease in blood pressure may occur. 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, (the L-isomer of ofloxacin), the infusion must be halted immediately.

Sodium content

This product contains 7.8 mmol (181 mg) sodium per 50 ml dose and 15.8 mmol (363 mg) per 100 ml dose. To be taken into consideration by patients on a controlled sodium diet.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently affects the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture (sometimes bilateral) can occur within the first 48 hours after the start of treatment and have been reported up to several months after discontinuation of treatment. The risk of tendinitis or tendon rupture is increased in patients over 60 years of age, in patients on daily doses of 1000 mg and when treating with corticosteroids. The daily dose should be adjusted in elderly patients according to creatinine clearance (see section 4.2). Following prescription of levofloxacin, these patients should therefore be closely monitored. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately and the affected tendon treated accordingly (e.g. immobilisation) (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 the end of treatment), may be indicative of *Clostridium difficile*-associated disease (CDAD). CDAD may range in severity from mild to its most severe (life-threatening) form, i.e. pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis if serious diarrhoea develops in patients during or after treatment with levofloxacin. If CDAD is suspected or confirmed, treatment with levofloxacin must be halted immediately and appropriate treatment initiated. Antiperistaltic agents are contraindicated in such cases.

Patients predisposed to seizures

Quinolones can lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with known epilepsy (see section 4.3) and, as with other quinolones, should be used only with extreme caution in patients predisposed to epileptic seizures or receiving concomitant treatment with medicinal products that lower the seizure threshold, such as theophylline (see section 4.5). If convulsive seizures occur (see section 4.8), treatment with levofloxacin should be discontinued.

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with latent or existing glucose-6-phosphate dehydrogenase deficiency may be prone to haemolytic reactions when treated with quinolones. When treating such patients with levofloxacin, potential occurrence of haemolysis should therefore be closely monitored.

Patients with impaired renal function

Since levofloxacin is excreted mainly by the kidneys, the dose should be adjusted in patients with impaired renal function (see section 4.2).

Hypersensitivity reactions

Levofloxacin can induce serious, potentially life-threatening hypersensitivity reactions (e.g. angioedema and even anaphylactic shock), occasionally even after the first dose (see section 4.8). Patients should discontinue treatment immediately and inform their physician or an emergency physician, 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 consult their doctor immediately if skin and/or mucosal reactions occur, prior to continuing treatment.

Dysglycaemia

As with all quinolones, abnormal blood glucose levels (including hyperglycaemia and hypoglycaemia) have been reported, usually in diabetics receiving concomitant treatment with an oral antidiabetic (e.g. glibenclamide) or with insulin. There are known cases of hypoglycaemic coma. In diabetic patients, careful monitoring of blood glucose levels 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) during and for up to 48 hours after treatment, in order to avoid photosensitisation.

Patients on treatment with vitamin K antagonists

Due to possible elevation of coagulation values (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with vitamin K antagonists (e.g. warfarin), coagulation values should be monitored when these medicines are used concomitantly (see section 4.5).

Psychotic reactions

Psychotic reactions have been reported in patients on treatment with 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). If any patient should develop such reactions, levofloxacin must be discontinued and appropriate measures instituted. Caution is indicated when using levofloxacin in psychotic patients or those with a history of psychiatric illness.

QT interval prolongation

Fluoroquinolones, including levofloxacin, should only be used with caution in patients with known risk factors for prolongation of the QT interval such as, for example:

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

Elderly patients and women may be more sensitive to QTc-prolonging medications. Fluoroquinolones, including levofloxacin, should therefore be used with caution in these patients (see sections 4.2 “Elderly patients”, 4.5, 4.8, and 4.9).

Peripheral neuropathy

Peripheral sensory neuropathy or peripheral sensory motor neuropathy has been reported in patients on treatment with fluoroquinolones, including levofloxacin, which can be rapid in its onset (see section 4.8). If patients develop symptoms of neuropathy, levofloxacin should be discontinued to prevent the development of irreversible damage.

Hepatobiliary disorders

Cases of hepatic necrosis and even fatal hepatic failure have been reported with levofloxacin, especially in patients with severe underlying diseases/comorbidities, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and

consult their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus and tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, may trigger neuromuscular blockade and exacerbate muscle weakness in patients with myasthenia gravis. Severe postmarketing adverse reactions (including death or the requirement for respiratory support) are associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is therefore not recommended for patients with known myasthenia gravis.

Visual disturbances

If vision becomes impaired or other effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Superinfection

In prolonged treatment with levofloxacin, overgrowth of non-susceptible organisms may occur. In the event of superinfection, appropriate measures should be undertaken.

Interference with laboratory results

In patients treated with levofloxacin, opiate detection in urine may give false-positive results. Positive results may have to be confirmed by more specific methods.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and hence lead to false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Tavanic

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs

No pharmacokinetic interactions of levofloxacin were demonstrated with theophylline in a clinical study. However, a pronounced lowering of the seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs or other agents that lower the cerebral seizure threshold. Levofloxacin concentrations were about 13% higher during co-medication with 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%), as both medicines are capable of blocking the renal tubular secretion of levofloxacin. However, at the doses tested in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Levofloxacin should be used with caution when co-administering medicinal products that affect tubular renal secretion, e.g. probenecid and cimetidine. This particularly applies to patients with renal insufficiency.

Other information

In clinical pharmacology studies, no clinically relevant effect on the pharmacokinetics of levofloxacin was shown when the following medicinal products were co-administered: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of Tavanic on other medicinal products

Ciclosporin

The half-life of ciclosporin was prolonged by 33% upon co-administration of levofloxacin.

Vitamin K antagonists

Prolongation of the prothrombin time (increase in INR/decrease in thromboplastin time) and/or even bleeding have been reported in patients concurrently treated with levofloxacin and vitamin K antagonists (e.g. warfarin). Such bleeding may even be severe. Coagulation values should therefore be monitored in patients treated with vitamin K antagonists (see section 4.4).

Medicinal products known to prolong the QT interval

Levofloxacin, like other fluoroquinolones, should only be used with caution in patients concurrently taking other medicinal products 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 information

A pharmacokinetic study showed that levofloxacin exerts no effect on the pharmacokinetics of theophylline (a test substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are only few data on the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Nevertheless, levofloxacin must not be used in pregnant women, as studies in humans are lacking and experimental data in animals indicate the risk of possible damage by fluoroquinolones to the cartilage tissue of weight-bearing joints in growing animals (see sections 4.3 and 5.3).

Breast-feeding

Tavanic is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human breast milk; however, other fluoroquinolones are known to be excreted in breast milk. Due to the lack of studies in humans and because experimental data in animals indicate a risk of possible damage by fluoroquinolones to the cartilage tissue of weight-bearing joints in growing animals, levofloxacin must not be used in breast-feeding women (see sections 4.3 and 5.3).

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. light-headedness/dizziness, drowsiness, visual disturbances) may impair the patient’s ability to concentrate and react, and may therefore constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

4.8 Undesirable effects

The following information is based on data from clinical studies with more than 8300 patients and on extensive post-marketing experience.

Frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

See table on page 4

Other undesirable effects that have occurred with fluoroquinolones:

- porphyria attacks in patients with porphyria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: http://www.bfarm.de

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies with supratherapeutic doses, the most important symptoms to be expected following acute overdose of Tavanic solution for infusion are central nervous symptoms (confusion, light-headedness, impairment of consciousness and seizures) and prolongation of the QT interval.

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from available data)
Infections and infestations		Fungal infection including Candida infection, pathogen resistance		
Blood and lymphatic system disorders		Leukopenia, eosinophilia	Thrombocytopenia, neutropenia	Pancytopenia, agranulocytosis, haemolytic anaemia
Immune system disorders			Angioedema, hypersensitivity reactions (see section 4.4)	Anaphylactic shock[a], anaphylactoid shock[a] (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia, particularly in diabetics (see section 4.4)	Hyperglycaemia, hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety, confusion, nervousness	Psychotic reactions (with e.g. hallucinations, paranoia), depression, agitation, abnormal dreams nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or actions (see section 4.4)
Nervous system disorders	Headache, light-headedness	Drowsiness, tremor, dysgeusia	Seizures (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 disorders, 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, palpitations	Ventricular tachycardia, which can lead to cardiac arrest, ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolongation (see sections 4.4 and 4.9)
Vascular disorders	*(after IV administration only):* Phlebitis		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm, allergic pneumonitis
Gastrointestinal disorders	Diarrhoea, vomiting. nausea	Abdominal pain, dyspepsia, flatulence, constipation		Haemorrhagic diarrhoea, which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4), pancreatitis
Hepatobiliary disorders	Elevated liver enzyme values (ALT/AST, alkaline phosphatase, GGT)	Elevated bilirubin values		Jaundice and severe liver injury, including cases with fatal acute liver failure, especially in patients with severe underlying diseases (see section 4.4), hepatitis
Skin and subcutaneous tissue disorders[b]		Exanthema, pruritus, urticaria, hyperhidrosis		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity reactions (see section 4.4), leukocytoclastic vasculitis, stomatitis

Continued on page 5

Table continued

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from available data)
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 particular importance in patients with myasthenia gravis (see section 4.4)	Rhabdomyolysis, tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4), ligament rupture, muscle rupture, arthritis
Renal and urinary disorders		Elevated serum creatinine values	Acute renal failure (e.g. in cases of interstitial nephritis)	
General disorders and administration site conditions	*(After IV administration only):* Infusion site reactions (pain, reddening)	Asthenia	Pyrexia	Pain (including pain in back, chest and extremities)

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

CNS effects (including confusion, seizures, hallucinations and tremor) have been observed in post-marketing experience.

In the event of an overdose, symptomatic treatment should be instituted. ECG monitoring should be undertaken due to the possible occurrence of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are unable to eliminate levofloxacin effectively. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones, ATC code: J01MA12
Levofloxacin is a synthetic antibiotic of the fluoroquinolone group. It is the S (-) enantiomer of the racemate ofloxacin.

Mechanism of action

As a fluoroquinolone antibiotic, levofloxacin acts on the DNA-DNA gyrase complex and topoisomerase IV.

Pharmacokinetic/pharmacodynamic relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum serum concentration (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance

Resistance to levofloxacin is acquired through stepwise mutations at the target site 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 has been observed.
Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other antibiotic classes.

Breakpoints for susceptibility testing

The EUCAST recommended breakpoints for levofloxacin, used to differentiate susceptible from intermediately susceptible pathogens and intermediately susceptible from resistant pathogens, are presented in the following table for MIC testing (in mg/l).

Clinical MIC breakpoints for levofloxacin according to EUCAST (version 2.0, 2012-01-01):

Pathogen	Susceptible	Resistant
Enterobacteriaceae	≤1 mg/l	>2 mg/l
Pseudomonas spp.	≤1 mg/l	>2 mg/l
Acinetobacter spp.	≤1 mg/l	>2 mg/l
Staphylococcus spp.	≤1 mg/l	>2 mg/l
S. pneumoniae [1]	≤2 mg/l	>2 mg/l
Streptococcus A, B, C, G	≤1 mg/l	>2 mg/l
H. influenzae [2, 3]	≤1 mg/l	>1 mg/l
M. catarrhalis [3]	≤1 mg/l	>1 mg/l
Non-species-specific breakpoints [4]	≤1 mg/l	>2 mg/l

1. The breakpoints relate to high-dose therapy.
2. Low-level fluoroquinolone resistance (ciprofloxacin MIC is 0.12 to 0.5 mg/l) may occur, but there is no indication that this resistance is of clinical importance in respiratory tract infections with *H. influenzae*.
3. Strains with MIC values above the "susceptible" breakpoint are very rare or not yet reported. The identification and susceptibility testing of any such isolate must be repeated. If the result is confirmed, the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for these confirmed isolates with MIC values above the "resistant" breakpoint, they are to be reported as resistant.
4. Breakpoints relate to oral or intravenous doses of 1 – 2 x 500 mg.

The prevalence of acquired resistance may vary geographically and with time for individual species. Local information on the resistance situation is therefore desirable, particularly for the adequate treatment of severe infections. Expert therapeutic advice should be sought when the local resistance situation is such that the efficacy of levofloxacin in at least some types of infection is questionable.

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

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

[#] Methicillin-resistant *S. aureus* 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 achieved within about 1 to 2 hours. The absolute bioavailability is 99 to 100%.

Food intake has only a minor effect on the absorption of levofloxacin.

Steady state is reached within 48 hours at a dosage of 500 mg once or twice daily.

Distribution

Approximately 30 to 40% of levofloxacin is bound to serum proteins.

The mean volume of distribution is approximately 100 l after single and repeated administration of 500 mg levofloxacin and indicates widespread distribution into body tissues.

Penetration into tissue and body fluids

Levofloxacin penetrates into bronchial mucosa, pulmonary surfactant film, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, penetration of levofloxacin into cerebrospinal fluid is poor.

Biotransformation

Levofloxacin is metabolised only to a very minor extent. The metabolites desmethyl-levofloxacin and levofloxacin N-oxide represent less than 5% of the dose excreted with the urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Following oral and intravenous administration of levofloxacin, the substance is eliminated relatively slowly from the plasma ($t_{½}$: 6 – 8 hours). Excretion is primarily by the renal route (>85% of the administered dose).

The mean apparent clearance of levofloxacin following a single 500 mg dose was 175 ± 29.2 ml/min.

There are no major differences with regard to the pharmacokinetics of levofloxacin after intravenous or oral administration, suggesting that the oral and intravenous routes of administration are interchangeable.

Linearity

Levofloxacin shows linear pharmacokinetics within the dose range of 50 to 1000 mg.

Special patient groups

Patients with impaired renal function
The pharmacokinetics of levofloxacin are affected by renal dysfunction. With decreasing renal function, renal elimination and clearance are reduced and elimination half-lives are increased (see table).

Pharmacokinetics in renal insufficiency following single oral 500 mg dose:

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 with regard to pharmacokinetics between young and elderly patients, apart from those associated with altered creatinine clearance.

Gender differences
A separate analysis for male and female subjects showed small to marginal differences in the pharmacokinetics of levofloxacin. There are no indications that these gender-specific differences are of clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans (based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenicity and toxicity to reproduction and development).

Levofloxacin caused no impairment of fertility or reproductive performance in rats and delayed maturation was seen as the only effect of maternal toxicity.

Levofloxacin induced no gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells *in vitro*. This can be attributed to inhibition of topoisomerase II. *In vivo* tests (micronucleus, sister chromatid exchange, UDS, dominant lethal tests) revealed no genotoxicity.
Only at very high doses did levofloxacin show a phototoxic potential in mice. Levofloxacin showed no genotoxic potential in a photomutagenicity assay and it reduced tumour development in a photocarcinogenicity study.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These effects were more marked in young animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid 36% (for pH adjustment)
Water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with heparin or alkaline solutions (e.g. sodium bicarbonate).
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Shelf life after perforation of the rubber stopper: use immediately (see section 6.6).

From a microbiological point of view, the opened solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.
Inspect visually prior to use. Only clear solutions without particles should be used.

6.5 Nature and contents of container

50 ml type I glass bottle with aluminium closure, chlorobutyl rubber stopper and tear-off polypropylene lid. The bottle contains 50 ml solution for infusion. Packs of 1 and 5 bottles.

100 ml type I glass bottle with aluminium closure, chlorobutyl rubber stopper and tear-off polypropylene lid. The bottle contains 100 ml solution for infusion. Packs of 1, 5 and 20 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Tavanic solution for infusion should be used immediately (within 3 hours) after perforation of the rubber stopper, in order to prevent any bacterial contamination.

No protection from light is necessary during the infusion.
This medicinal product is for single use only.
The solution should be visually inspected prior to use. The solution may only be used if it is clear, yellowish-green solution and free from particles.
Any unused medicinal product should be disposed of in accordance with local requirements.

Miscibility with other solutions for infusion

Tavanic solution for infusion is compatible with the following solutions for infusion:
- 0.9% NaCl solution,
- 5% glucose injection,
- 2.5% glucose Ringer's solution,
- Combination solutions for parenteral nutrition (amino acids, glucose, electrolytes).

See also section 6.2 "Incompatibilities".

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main

Postal address:
Postfach (PO box) 80 08 60
65908 Frankfurt am Main

Tel.: (01 80) 2 22 20 10*
Fax: (01 80) 2 22 20 11*
E-mail: medinfo.de@sanofi.com

8. MARKETING AUTHORISATION NUMBER

41384.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 1998
Date of latest renewal: 31 July 2012

10. DATE OF REVISION OF THE TEXT

May 2013

GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription

Pack sizes available in Germany:
Original pack with 1 bottle of 50 or 100 ml
Hospital pack with 5 bottles of 50 or 100 ml

* €0.06 per call (German landline); max. €0.42/min (mobile networks).

Direct all enquiries to:
Rote Liste Service GmbH
FachInfo-Service ≈ SmPC Department
PO Box 11 01 71
10831 Berlin