sanofi aventis

Because health matters

2 ספטמבר 2013

סאנופי-אוונטיס ישראל בע"מ

שם התכשיר:

TAVANIC 500MG solution for I.V. infusion (1194329962)

חומר פעיל:

Levofloxacin (as hemihydrate) 5 mg/ml

ההתוויה המאושרת הינה:

In adults for whom intravenous therapy is considered to be appropriate, Tavanic solution for infusion is indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Community-acquired pneumonia.
- Complicated urinary tract infections including pyelonephritis.
- Skin and soft tissue infections.

חברת סאנופי אוונטיס ישראל בע"מ מבקשת להודיע על עדכון העלון לרופא בחודש יוני 2013.

שימו לב! בהמשך להרמוניזציה של עלוני התכשירים המכילים levofloxacin באירופה, עודכן בין השאר סעיף **המינון** בעלון.

העלונים בהם מסומנים העדכונים מצורפים להודעה זו.
מידע חדש מסומן בצהוב.
מידע שהוסר/הוחלף מסומן באדום עם קו מחיקה.
מידע שהינו שינוי עריכה או מיקום בעלון מסומן בירוק.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום , סאנופי-אוונטיס ישראל בע"מ, רח' בני גאון 10 נתניה או בטלפון : 09-8633700 .

מצורף הקישור לאתר משרד הבריאות http://www.health.gov.il/units/pharmacy/trufot/index.asp.

בברכה,
ויקטוריה גוטלויבר-הדדי

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו ביוני 2013

Tavanic 500mg solution for I.V. infusion– Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Tavanic 500mg solution for I.V. infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg of levofloxacin (as hemihydrate) in a 100 ml glass bottle

One ml of solution for infusion contains 5 mg of levofloxacin (as hemihydrate)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults for whom intravenous therapy is considered to be appropriate, Tavanic solution for infusion is indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

• Community-acquired pneumonia.

• Complicated urinary tract infections including pyelonephritis.

• Skin and soft tissue infections.

Before prescribing Tavanic, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolones.

4.2 Posology and method of administration

Tavanic solution for infusion is administered by slow intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility ~~sensitivity~~ of the presumed causative pathogen. ~~It is usually possible to switch from initial intravenous treatment to the oral route after a few days (Tavanic 250 or 500 mg tablets), according to the condition of the patient.~~ Treatment with Tavanic after initial use of the intravenous preparation may be completed with an appropriate oral presentation according to the SPC for the film-coated tablets and as

considered appropriate for the individual patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

~~***Duration of treatment***~~

~~The duration of treatment varies according to the course of the disease. As with antibiotic therapy in general, administration of Tavanic (solution for infusion or tablets) 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.~~

Posology

The following dose recommendations can be given for Tavanic:

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

Indication	**Daily dose regimen** *(according to severity)*	**Total duration of treatment**[1] *(according to severity)*
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Pyelonephritis	~~250~~[1] 500 mg once daily	7 - 10 days
Complicated urinary tract infections	~~250~~[1] 500 mg once daily	7 - 14 days
Skin and soft tissue infections	500 mg once or twice daily	7 - 14 days

~~[1]Consideration should be given to increasing the dose in cases of severe infection.~~

[1] Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous to oral treatment depends on the clinical situation but is normally 2 to 4 days.

Special populations

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

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

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

Impaired liver function

No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

~~*In the elderly*~~ ***Elderly population***

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

~~*In children*~~ ***Paediatric population***

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

Method of administration

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

~~It is possible to switch from an initial intravenous application to the oral route at the same dosage after a few days, according to the condition of the patient.~~

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

4.3 Contraindications

Tavanic solution for infusion must not be used:

- in patients hypersensitive to levofloxacin or any other quinolone and any of the excipients listed in section 6.1,
- 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 Tavanic may not be the optimal therapy.~~

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

Methicillin-resistant *S. aureus* is very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, levofloxacin is not recommended for the treatment of known or suspected MRSA-infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents 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 the European Union. 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 60 minutes for 500 mg TAVANIC 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 15.8 mmol sodium (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 involves the Achilles tendon and may lead to tendon rupture. ~~This undesirable effect~~ Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting of treatment ~~and may be bilateral~~ with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in ~~the elderly~~ patients aged over 60 years, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance (see section 4.2). Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin ~~Tavanic~~. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin ~~Tavanic~~ must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon (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. ~~If pseudomembranous colitis is suspected,~~ If CDAD is suspected or confirmed, levofloxacin should ~~must~~ be stopped immediately and ~~patients should be treated with supportive measures ± specific therapy without delay (e.g. oral vancomycin)~~ appropriate treatment initiated without delay. ~~Products inhibiting the peristalsis~~ Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. ~~Tavanic solution for infusion are~~ 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

receiving ~~such as patients with pre-existing central nervous system lesions,~~ concomitant treatment with active substances that ~~fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs 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 agents~~, and so levofloxacin should be used with caution~~. 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 Tavanic 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.

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.

~~*Hypoglycemia*~~ ***Disglycaemia***

As with all quinolones, ~~hypoglycemia has~~ 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~~ Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. (see section 4.8).

Prevention of photosensitisation

~~Although photosensitisation is very rare~~ 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 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 ~~Tavanic~~ in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly (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)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

(See section 4.2 Elderly population, ~~section~~ 4.5, ~~section~~ 4.8~~, section~~ and 4.9).

Peripheral neuropathy

~~Sensory or sensorimotor peripheral neuropathy has~~ 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~~ 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 ~~Tavanic~~ , have neuromuscular blocking activity and may exacerbate muscle weakness in ~~persons~~ patients with myasthenia gravis. Postmarketing serious adverse ~~events~~ reactions, including deaths and the requirement for ~~ventilatory~~ respiratory support, have been associated with fluoroquinolone use in ~~persons~~ patients with myasthenia gravis. ~~Avoid~~ Levofloxacin ~~Tavanic~~ 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

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

Interference with laboratory tests

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Effect of other medicinal products on Tavanic

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

Effect of Tavanic on other medicinal products

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

~~Reproductive studies in animals did not raise specific concern.~~ There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However, in the absence of

human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin ~~Tavanic~~ must not be used in pregnant women (see sections 4.3 and 5.3).

~~*Lactation*~~ ***Breast-feeding***

Tavanic is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however, other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, ~~Tavanic solution for infusion~~levofloxacin must not be used in breast-feeding women (see section 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. 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 ~~5000~~8300 patients and on extensive post marketing experience.

~~The adverse reactions are described according to the MedDRA system organ class in the table below.~~

Frequencies in this table are defined using the following convention: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, ~~≤~~ <1/100), rare (≥ 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 (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10000)	Not known (cannot be estimated from available data)
Infections and infestations		Fungal infection ~~(and proliferation of other resistant microorganisms)~~ including Candida infection Pathogen resistance			
Blood and the lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	~~agranulocytosis~~	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)	~~Anaphylactic shock~~	~~Hypersensitivity (see section 4.4)~~ Anaphylactic shock [a] Anaphylactoid shock [a] (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)	~~Hypoglycemia, particularly in diabetic patients (see section 4.4)~~	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	~~Insomnia~~ Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression ~~Confusional state~~ Agitation Abnormal dreams Nightmares ~~Anxiety~~	~~Psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4) hallucination~~	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)

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** (<1/10000)	**Not known (cannot be estimated from available data)**
Nervous system disorders	Headache Dizziness	~~Dizziness, headache~~ Somnolence Tremor Dysgeusia	Convulsion (see sections 4.3 and 4.4) ~~tremor~~ Paraesthesia	~~sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia~~, ~~parosmia including anosmia~~	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)	~~Visual disturbance~~	Transient vision loss (see section 4.4)
Ear and labyrinth disorders		Vertigo	Tinnitus	~~Hearing impaired~~	~~Tinnitus~~ Hearing loss Hearing impaired

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** (<1/10000)	**Not known (cannot be estimated from available data)**
Cardiac disorders			Tachycardia Palpitation		Ventricular tachycardia, 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 ~~QT interval prolongation~~ and 4.9)
Vascular disorders	*Applies to iv form only:* Phlebitis		Hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea	~~Bronchospasm,~~ ~~Dyspnoea~~	~~Pneumonitis allergic~~	Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	~~Vomiting~~ Abdominal pain Dyspepsia Flatulence Constipation	~~Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis~~		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis

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** (<1/10000)	**Not known (cannot be estimated from available data)**
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		~~Hepatitis~~	Jaundice and severe liver injury, including fatal cases with acute liver failure, ~~has been reported with levofloxacin,~~ primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash Pruritus Urticaria Hyperhidrosis	~~Urticaria~~	~~Angioneurotic oedema~~, ~~photosensitivity reaction~~	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme ~~hyperhidrosis~~ Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis

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 (<1/10000)	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 special importance in patients with myasthenia gravis (see section 4.4) ~~Arthralgia,~~ ~~Myalgia~~	~~Tendon rupture (see section 4.4).~~ ~~This undesirable effect may occur within 48 hours of starting treatment and may be bilateral,~~ ~~muscular weakness which may be of special 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		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	~~Renal failure acute (e.g. due t~~ ~~nephritis interstitial)~~	
General disorders and administration site conditions	*Applies to iv form only:* Infusion site reaction (pain, reddening)	Asthenia	Pyrexia	~~Pyrexia~~	Pain (including pain in back, chest, and extremities)

[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 effect~~s~~ which have been associated with fluoroquinolone administration include**s**:

~~• extrapyramidal symptoms and other disorders of muscular coordination,~~

~~• hypersensitivity vasculitis,~~

• 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 Tavanic solution for infusion 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.

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

Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones , ATC code: J01MA12

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

Mechanism of action

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

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

~~The main mechanism of resistance is due to a *gyr A* mutation. *In vitro* there is a cross-resistance between levofloxacin and other fluoroquinolones.~~

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/~~L~~l).

EUCAST clinical MIC breakpoints for levofloxacin ~~(2006-06-20)~~ (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 related breakpoints [4]	≤1 mg/l	>2 mg/l

1. ~~The S/I breakpoint was increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution.~~ The breakpoints for levofloxacin relate to high dose therapy.

2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence 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 antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint, they should be reported resistant.

4. ~~Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where susceptibility testing is not recommended or for which there is insufficient evidence that the species in question is a good target (Enterococcus, Neisseria, Gram negative anaerobes).~~ Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

~~The CLSI (Clinical And Laboratory Standards Institute, formerly NCCLS)recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (µg/mL) or disc diffusion testing (zone diameter [mm] using a 5 µg levofloxacin disc).~~

~~CLSI recommended MIC and disc diffusion breakpoints for levofloxacin (M100-S17, 2007):~~

~~Pathogen~~	~~Susceptible~~	~~Resistant~~

~~Enterobacteriaceae~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~
~~Non Enterobacteriaceae.~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~
~~*Acinetobacter spp.*~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~
~~*Stenotrophomonas maltophilia*~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~
~~*Staphylococcus spp.*~~	~~≤ 1 µg/mL~~ ~~≥ 19 mm~~	~~≥ 4 µg/mL~~ ~~≤ 15 mm~~
~~*Enterococcus spp.*~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~
~~*H.influenzae M.catarrhalis* [1]~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	- -
~~*Streptococcus pneumoniae*~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~
~~*beta-hemolytic Streptococcus*~~	~~≤ 2 µg/mL~~ ~~≥ 17 mm~~	~~≥ 8 µg/mL~~ ~~≤ 13 mm~~

~~[1] The absence or rare occurrence of resistant strains precludes defining any results categories other than « susceptible ». for strains yielding results suggestive of a « nonsuceptible » category, organism identification and antimicrobial susceptibility test results should be confirmed by a reference laboratory using CLSI reference dilution method.~~

~~Antibacterial spectrum~~

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

Commonly susceptible species

Aerobic Gram-positive bacteria

Bacillus anthracis

Staphylococcus aureus~~*~~ *methicillin-susceptible*

Staphylococcus saprophyticus

Streptococci, *group C and G*

Streptococcus agalactiae

*Streptococcus pneumoniae**

*Streptococcus pyogenes**

Aerobic Gram- negative bacteria

~~*Burkholderia cepacia $*~~

Eikenella corrodens

*Haemophilus influenzae**

*Haemophilus para-influenzae**

Klebsiella oxytoca

~~*Klebsiella pneumoniae**~~

*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 agglomerans*~~

Enterobacter cloacae~~*~~

Escherichia coli~~*~~

Klebsiella pneumoniae

Morganella morganii~~*~~

Proteus mirabilis~~*~~

Providencia stuartii

Pseudomonas aeruginosa~~*~~

Serratia marcescens ~~*~~

Anaerobic bacteria

Bacteroides fragilis

~~*Bacteroides ovatus$*~~

~~*Bacteroides thetaiotamicron$*~~

~~*Bacteroides vulgatus$*~~

~~*Clostridium difficile$*~~

Inherently resistant strains

Aerobic Gram-positive bacteria

Enterococcus faecium

~~*Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications~~

~~$Natural intermediate susceptibility~~

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

~~**Other information**~~

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

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 ~~approximately~~ 99-100 %.

Food has little effect on the absorption of levofloxacin.

Steady-state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein.

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

~~500 mg once daily multiple dosing 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 3 days.~~

Penetration into tissues and body fluids:

~~*Penetration into Bronchial Mucosa, Epithelial Lining Fluid (ELF)*~~

~~Maximum levofloxacin concentrations in bronchial mucosa and epithelial lining fluid after 500 mg p.o. were 8.3 µg/g and 10.8 µg/ml respectively. These were reached approximately one hour after administration.~~

~~*Penetration into Lung Tissue*~~

~~Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 µg/g and were reached between 4 and 6 hours after administration. The concentrations in the lungs consistently exceeded those in plasma.~~

~~*Penetration into Blister Fluid*~~

~~Maximum levofloxacin concentrations of about 4.0 and 6.7 µg/ml in the blister fluid were reached 2 - 4 hours after administration following 3 days dosing at 500 mg once or twice daily, respectively.~~

~~*Penetration into Cerebro-Spinal Fluid*~~

~~Levofloxacin has poor penetration intro cerebro-spinal fluid.~~

~~*Concentration in urine*~~

~~The mean urine concentrations 8 -12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91 mg/L and 200 mg/L, respectively.~~

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebro-spinal fluid.

~~**Metabolism**~~ **Biotransformation**

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ($t_{½}$: 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 ~~600~~1000 mg.

Special populations

Subjects with renal insufficiency

The pharmacokinetics of levofloxacin isare affected by renal impairment. With decreasing renal function, renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Clcr [ml/min]	<20	20 - ~~40~~49	50 – 80
ClR [ml/min]	13	26	57
t1/2 [h]	35	27	9

Elderly subjects

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

Gender differences

Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data

~~**Acute toxicity**~~

~~The median lethal dose (LD_{50}) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg.~~

~~Administration of 500 mg/kg p.o. to monkeys induced little effect apart from vomiting.~~

~~**Repeated dose toxicity**~~

~~Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg/kg/day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100 mg/kg/day and 10, 25, 62.5 mg/kg/day for 1 and 6 months in the monkey.~~

~~Signs of reaction to treatment were minor in the rat with slight effects principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters. The No Observed Adverse Effect Levels (NOELs) in these studies were concluded to be 200 and 20 mg/kg/day after 1 and 6 months respectively.~~

~~Toxicity after oral dosing in the monkey was minimal with reduced body weight at 100 mg/kg/day together with salivation, diarrhoea and decreased urinary pH in some animals at this dose. No toxicity was seen in the 6 month study. The NOELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.~~

~~The NOELs in the six month studies were concluded to be 20 and 62.5 mg/kg/day in the rat and monkey respectively.~~

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

~~Reproductive toxicity~~

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity. ~~at oral doses as high as 360 mg/kg/day or intravenous doses up to 100 mg/kg/day.~~

~~Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 50 mg/kg/day or intravenously with up to 25 mg/kg/day.~~

~~Genotoxicity~~

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells *in vitro* ~~at or above 100 µg/ml, in the absence of metabolic activation~~. These effects can be attributed to inhibition of topoisomerase II. *In vivo* tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

~~Phototoxic potential~~

Studies in the mouse ~~after both oral and intravenous dosing~~ showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenity ~~assay~~ study.

~~Carcinogenic potential~~

~~No indication of carcinogenic potential was seen in a two year study in the rat with dietary administration (0, 10, 30 and 100 mg/kg/day).~~

~~Toxicity to joints~~

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

~~Tavanic 5 mg/ml solution for infusion contains the following excipients:~~

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid concentrated (for pH adjustment) ~~*(qs:* pH 4.8*) and*~~

Water for injection. ~~(Na $^{+}$ concentration: 154 mmol / L).~~

6.2 Incompatibilities

Tavanic 5 mg/ml solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium ~~hydrogen carbonate~~bicarbonate). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

~~Shelf life as packaged for sale:~~ 3 years

~~Shelf life after removal of the outer packaging: 3 days (under indoor light conditions).~~

Shelf life after perforation of the rubber stopper: immediate use (within 3 hours) (see section 6.6) ~~3 hours (see 6.6).~~

Shelf life after removal of the outer packaging: 3 days (under indoor light conditions).

From a microbiological point of view, the 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 container in the outer carton in order to protect from light (see section 6.3).

Inspect visually prior to use. Only clear solutions without particles should be used.

6.5 Nature and contents of container

100 ml, type 1 glass bottle with flanged aluminium cap, chlorobutyl rubber stopper and tear-off polypropylene lid. Each bottle contains 100 ml solution.

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 infusion.

This medicinal product is for single use only.

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

As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.

Mixture with other solutions for infusion:

Tavanic solution for infusion is compatible with the following solutions for infusion:

- 0.9 % sodium chloride solution USP.
- 5 % dextrose injection USP.
- 2.5 % dextrose in Ringer solution.
- Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

See 6.2 for incompatibilities.

7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel ltd.

10 Beni Gaon, POB 8090, Netanya

8. MANUFACTURER

Sanofi-Aventis **Deutschland GmbH** Germany