sanofi aventis
Because health matters

**4 יולי 2011**

**סאנופי-אוונטיס ישראל בע"מ**

**שם התכשיר:**

**TAVANIC Injection 500MG 1194329962**
**TAVANIC Tablets 250MG 1194529964**
**TAVANIC Tablets 500MG 1194429963**

**חומר פעיל:**

**Levofloxacin (as hemihydrate) 5 mg/ml**
**Levofloxacin (as hemihydrate) 250 mg**
**Levofloxacin (as hemihydrate) 500 mg**

**ההתוויה המאושרת הינה:**

**Injection:**
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.

**Tablets:**
In adults with infections of mild or moderate severity, Tavanic tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:
• Acute sinusitis
• Acute exacerbations of chronic bronchitis
• Community-acquired pneumonia
• Complicated urinary tract infections including pyelonephritis
• Skin and soft tissue infections.

חברת סאנופי אוונטיס מבקשת להודיע על עדכון העלונים לרופא ולצרכן בחודש מאי 2011.
העלונים בהם מסומנים העדכונים מצורפים להודעה זו.
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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,

עירית זאב
רוקחת ממונה

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פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידי

עלון מאושר
5.11.

**Tavanic IV – Prescribing Information**

## 1. NAME OF THE MEDICINAL PRODUCT

Tavanic Injection 500mg ~~5 mg/ml~~ solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg of levofloxacin in a 100 ml glass bottle

One ml of solution for infusion contains 5 mg of levofloxacin

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 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. 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.

***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.

***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)* |
|---|---|
| Community-acquired pneumonia | 500 mg once or twice daily |
| Complicated urinary tract infections including pyelonephritis | 250 mg[1] once daily |
| Skin and soft tissue infections | 500 mg twice daily |

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

***Special populations***

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

| | **Dose regimen** | | |
|---|---|---|---|
| | **250 mg/24 h** | **500 mg/24 h** | **500 mg/12 h** |
| **Creatinine clearance** | *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<br><br>(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***

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function (See section 4.4 QT interval prolongation).

***In children***

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

## 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,
• 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.

***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.

***Exacerbation of myasthenia gravis***

Fluoroquinolones, including Tavanic, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid Tavanic in patients with known history of myasthenia gravis

***Tendinitis and tendon rupture***

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. This undesirable effect may occur within 48 hours of starting of treatment and may be bilateral The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Tavanic. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Tavanic must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

***Clostridium difficile-associated disease***

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Tavanic solution for infusion, may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Tavanic solution for infusion must be stopped immediately and patients should be treated with supportive measures ± specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are

contraindicated in this clinical situation.

***Patients predisposed to seizures***

Tavanic solution for infusion are contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous system lesions, concomitant treatment with 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, 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.

***Superinfection***

As with other antibiotics, the use of TAVANIC, 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.

***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.

***Hypoglycemia***

As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic 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***

Although photosensitisation is very rare with levofloxacin, 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 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).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
(See section 4.2 *Elderl*y, section 4.5, section 4.8, section 4.9).

***Peripheral neuropathy***

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. 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.

## 4.5 Interaction 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 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). (See section 4.4 QT interval prolongation).

## 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, Tavanic must not be used in pregnant women (see section 4.3 and 5.3).

***Lactation***

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, Tavanic solution for infusion must not be used in breast-feeding women (see section 4.3 and 5.3).

## 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 5000 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.

**Infections and infestations**

Uncommon : Fungal infection (and proliferation of other resistant microorganisms)

**Blood and lymphatic system disorders**

Uncommon : Leukopenia, eosinophilia
Rare : Thrombocytopenia, neutropenia
Very rare : Agranulocytosis
Not Known : Pancytopenia, haemolytic anaemia

**Immune system disorders**

Very rare : Anaphylactic shock (see section 4.4)

*Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose*

Not known : Hypersensitivity (see section 4.4)

**Metabolism and nutrition disorders**

Uncommon : Anorexia
Very rare : Hypoglycemia, particularly in diabetic patients (see section 4.4)

**Psychiatric disorders**

Uncommon : Insomnia, nervousness
Rare : Psychotic disorder, depression, confusional state, agitation, anxiety
Very rare : Psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4), hallucination

**Nervous system disorders**

Uncommon : Dizziness, headache, somnolence
Rare : Convulsion, tremor, paraesthesia
Very rare : sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia.

**Eye disorders**

Very rare : Visual disturbance

**Ear and Labyrinth disorders**

Uncommon : Vertigo
Very rare : Hearing impaired
Not known : Tinnitus

**Cardiac disorders**

Rare : Tachycardia
Not Known : Electrocardiogram QT prolonged (see section 4.4 QT interval prolongation and section 4.9)

**Vascular disorders**

Common : Phlebitis
Rare : Hypotension

**Respiratory, thoracic and mediastinal disorders**

Rare : Bronchospasm, dyspnoea
Very rare : Pneumonitis allergic

**Gastrointestinal disorders**

Common : Diarrhoea, nausea
Uncommon : Vomiting, abdominal pain, dyspepsia, flatulence, constipation
Rare : Diarrhoea –haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis

**Hepatobiliary disorders**

Common : Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon : Blood bilirubin increased
Very rare : Hepatitis
Not known: Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases (see section 4.4).

**Skin and subcutaneous tissue disorders**

Uncommon : Rash, pruritus
Rare : Urticaria
Very rare : Angioneurotic oedema, photosensitivity reaction
Not Known : Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis
Mucocutaneous reactions may sometimes occur even after the first dose

**Musculoskeletal and Connective tissue disorders**

Rare : Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia
Very rare : 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)
Not Known : Rhabdomyolysis

**Renal and urinary disorders**

Uncommon : Blood creatinine increased
Very rare : Renal failure acute (e.g. due to nephritis interstitial)

**General disorders and administration site conditions**

Common : Infusion site reaction
Uncommon : Asthenia
Very rare : Pyrexia
Not known : Pain (including pain in back, chest, and extremities)

Other undesirable effects which have been associated with fluoroquinolone administration include:
• 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.
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 (Cmax) 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.

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).

EUCAST clinical MIC breakpoints for levofloxacin (2006-06-20):

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Enterobacteriacae | ≤ 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 M.catarrhalis* [2] | ≤ 1 mg/L | >1 mg/L |
| Non-species related breakpoints[3] | ≤ 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 relate to high dose therapy.

[2] Strains with MIC values above the S/I 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 sent to a reference laboratory.

[3] 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)

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<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| Non Enterobacteriaceae. | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *Acinetobacter spp.* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *Stenotrophomonas maltophilia* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |

| | | |
|---|---|---|
| *Staphylococcus spp.* | ≤ 1 µg/mL<br>≥ 19 mm | ≥ 4 µg/mL<br>≤ 15 mm |
| *Enterococcus spp.* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *H.influenzae*<br>*M.catarrhalis* [1] | ≤ 2 µg/mL<br>≥ 17 mm | |
| *Streptococcus pneumoniae* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *beta-hemolytic Streptococcus* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 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** |
| *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* * |
| *Morganella morganii* * |
| *Proteus mirabilis* * |
| *Providencia stuartii* |
| *Pseudomonas aeruginosa** |
| *Serratia marcescens* * |
| **Anaerobic bacteria** |
| *Bacteroides fragilis* |
| *Bacteroides ovatus$* |
| *Bacteroides thetaiotamicron$* |
| *Bacteroides vulgatus$* |
| *Clostridium difficile$* |

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

$ natural intermediate susceptibility

**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 h. The absolute bioavailability is approximately 100 %. Food has little effect on the absorption of levofloxacin.

### Distribution

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

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 po 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 into 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.

**Metabolism**

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

**Elimination**

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

**Subjects with renal insufficiency**

The pharmacokinetics of levofloxacin are 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:

| | | | |
|---|---|---|---|
| $Cl_{cr}$ [ml/min] | < 20 | 20 - 40 | 50 - 80 |
| $Cl_R$ [ml/min] | 13 | 26 | 57 |
| $t_{1/2}$ [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 intravenous administration of levofloxacin were in the range 250-400 mg/kg; in dogs the $LD_{50}$ value was approximately 200 mg/kg with one of two animals which received this dose dying.

### Repeated dose toxicity

Studies of one month duration with intravenous administration have been carried out in the rat (20, 60, 180 mg/kg/day) and monkey (10, 25, 63 mg/kg/day) and a three-month study has also been carried in the rat (10, 30, 90 mg/kg/day).
The “No Observed Adverse Effect Levels” (NOEL) in the rat studies were concluded to be 20 and 30 mg/kg/day in the one-month and three-month studies respectively. Crystal deposits in urine were seen in both studies at doses of 20 mg/kg/day and above. High doses (180 mg/kg/day for 1 month or 30 mg/kg/day and above for 3 months) slightly decreased food consumption and body weight gain. Haematological examination showed reduced erythrocytes and increased leucocytes and reticulocytes at the end of the 1 month, but not the 3 months study.
The NOEL in the monkey study was concluded to be 63 mg/kg/day with only minor reduction in food and water consumption at this dose.

### Reproductive toxicity

Levofloxacin caused no impairment of fertility or reproductive performance in rats 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.
Levofloxacin had no effect on fertility and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

### Genotoxicity

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung (CHL) cells *in vitro* at or above 100 μg/ml, in the absence of metabolic activation. *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 intravenous and oral 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 photocarcinogenicity assay.

### 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, hydrochloric acid *(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). 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:3 hours* (see 6.6).

From a microbiological point of view, the solution for infusion should be used immediately.

## 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

100ml, 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.

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.

## 8. MANUFACTURER

Sanofi-Aventis Germany

**פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידי**

**עלון מאושר**
**5.11.**

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו - 1986

תרופה זו חייבת במרשם רופא

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה:

שם התכשיר וצורתו: טאבניק טבליות 250 מ"ג , טאבניק טבליות 500 מ"ג.

הרכב: החומר(ים) הפעיל(ים) וכמותם/ריכוזם: Levofloxacin (as hemihydrate) 250mg
Levofloxacin (as hemihydrate) 500mg
חומרים בלתי פעילים :
Microcrystalline cellulose; MethylHydroxypropylcellulose; Crospovidone; Sodium stearylfumarate; Titanium dioxide; Macrogol 8000;Talc; Red & Yellow ferric oxide.

קבוצה תרפויטית: אנטיביוטיקה השייכת למשפחת הפלואורוקווינולונים.

פעילות רפואית :טיפול בזיהומים בקטריאלים הנגרמים ע"י חיידקים הרגישים ל- Levofloxacin .
לדוגמא: דלקת של הסינוסים, זיהומים במערכת הנשימה התחתונה, זיהומים בדרכי השתן ובכליות וכן זיהומים בעור וברקמות רכות.

מתי אין להשתמש בתכשיר?

| |
|---|
| אל תשתמשי בתרופה כאשר הינך בהריון מתכננת הריון או מניקה.<br>אין להשתמש אם ידועה רגישות ללבופלוקסצין, אנטיביוטיקה אחרת ממשפחת הקווינולינים או לאחד ממרכיבי התרופה.<br>אין להשתמש בחולים הסובלים ממחלת הנפילה (אפילפסיה).<br>התכשיר אינו מיועד לתינוקות, ילדים ומתבגרים.<br>אין להשתמש בחולים שסבלו בעבר מבעיות בגידים (כגון: דלקות בגידים) שנבעו מטיפול באנטיביוטיקה מקבוצת הפלואורוקווינולונים. |

אין להשתמש בתרופה מבלי להוועץ ברופא לפני התחלת הטיפול
אם ידוע לך על חוסר באנזים G6PD
אם הינך סובל/ת או סבלת בעבר מליקוי בתפקוד הכליה/מערכת השתן, כבד, מערכת העצבים, מפורפיריה , פגיעה מוחית ( כגון שבץ או נזק מוחי חמור), התכווציות, בעיות נפשיות, בעיות בלב, סוכרת, מחלה הגורמת לחולשת שרירים חמורה(myasthenia gravis)

איך תשפיע התרופה על חיי היום יום שלך?

| |
|---|
| השימוש בתרופה זו עלול לפגום בערנות ועל כן מחייב זהירות בנהיגה ברכב, בהפעלת מכונות מסוכנות ובכל פעילות המחייבת עירנות. באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקרבת הכביש וכדומה. |

תרופה זו עלולה לגרום לרגישות מיוחדת עם חשיפה לשמש ולאור אולטרה סגולי, על כן יש להמנע מחשיפה לשמש ולהדאוג להגנה מתאימה (בגדים ארוכים, כובע, משחות הגנה וכו')

אזהרות:
אם הינך רגיש/ה למזון כלשהו או לתרופה כלשהי, עליך להודיע על-כך לרופא לפני נטילת התרופה
במקרים נדירים טאבניק יכול לגרום לכאב ודלקת בגידים, בעיקר במטופלים מבוגרים או מטופלים הנוטלים קורטיקוסטרואידים. אם הנך חש בעיה כלשהי בגידים לאחר לקיחת התרופה אנא פנה לרופא מיד.

תרופות ממשפחת הפלואורוקווינולונים, בהן טאבניק, עלולות לגרום להחמרה של הסימפטומים של מחלת ה myasthenia gravis כגון החמרת חולשת השרירים או בעיות בנשימה – אם הנך חש בתופעות אלו פנה לרופא מיד.
בחולי סוכרת המטופלים בתכשירים נוגדי סוכרת פומיים או אינסולין יש לעקוב אחר רמות הסוכר בדם בזמן השימוש בטאבניק , קיימת האפשרות של קבלת תוצאות שגויות בבדיקת אופאיטים ~~opiates~~ בשתן.

<u>תגובות בין תרופתיות:</u>
אם הינך נוטל/ת תרופה נוספת כולל תרופות הנמכרות ללא מרשם רופא ותוספי תזונה,, או אם גמרת זה עתה הטיפול בתרופה אחרת עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות בין-תרופתיות. במיוחד, לגבי תרופות מהקבוצות הבאות:
-קורטיקוסטרואידים
אספירין ותרופות נוגדות דלקת לא סטרואידליות, תאופילין, פרובנציד, סימטידין, ציקלוספורין, מלחי ברזל, סותרי חומצה המכילים מגנזיום או אלומיניום, סוקראלפאט, ויטמין K אנטגוניסט כגון וורפרין (נגד קרישת דם), תרופות המשפיעות על פעילות הלב כגון: תרופות המשפיעות על קצב הלב (כגון: קווינידין , אמיאודארון) , תרופות לטיפול בדיכאון (כגון: אמיטרפטילין ואימיפרמין) ותרופות לטיפול בזיהומים (כגון : אנטיביוטיקות מקרולידיות כגון אריתרומיצין, אזיתרומיצין וקלריתרומיצין).

<u>תופעות לוואי:</u>
בנוסף לפעילות הרצויה של התרופה, בזמן השימוש בה עלולות להופיע השפעות לוואי כגון:

**שכיח: תופעות שיכולות להופיע בפחות מחולה 1 מתוך 10 חולים**
- בחילה , שלשול ,
- עליה ברמת אנזימי כבד בדם

**לא שכיח: תופעות שיכולות להופיע בפחות מחולה 1 מתוך 100 חולים**
- גרד ופריחה
- איבוד תאבון, הפרעות בעיכול, הקאה או כאב באזור הבטן, עצירות נפיחות בבטן(גזים)
- כאב ראש , סחרחורת, נמנום , בעיות בשינה, עצבנות,
- חריגות בתוצאות בדיקות דם עקב בעיות בכבד או בכלייה
- שינוי במספר תאי הדם הלבנים
- חולשה כללית
- כל טיפול אנטיביוטי שהורג חיידקים יכול לגרום לחוסר איזון במיקרואורגניזמים שבדרך כלל מצויים בגוף האדם. כתוצאה מכך, ייתכן ותגדל כמות המיקרואורגנזמים, דבר שבמקרים נדירים ידרוש טיפול רפואי.

**נדיר: תופעות שיכולות להופיע בפחות מחולה 1 מתוך 1,000 חולים**
- תחושת עקצוץ לדוגמא בידיים , רעד,
- חרדה, דיכאון, בעיות נפשיות, חוסר שקט, בלבול
- דפיקות לב מהירות, לחץ דם נמוך
- כאב מפרקים או כאב שרירים
- ירידה במספר טסיות הדם הגורמת לנטייה לחבורות ודימום
- רמה נמוכה של תאי דם לבנים ( נויטרופניה)
- קשיי נשימה , קוצר נשימה
- גרד חריף או אודם / נפיחות עורית ( אורטיקריה)

**נדיר ביותר : תופעות שיכולות להופיע בפחות מחולה 1 מתוך 10,000 חולים**
- עליה ברגישות העור לאור שמש ולאור אולטרה סגולי.
- ירידה ברמות הסוכר בדם לרמה נמוכה ( היפוגליקמיה) – חשוב בעיקר לחולי סוכרת
- בעיות בשמיעה וראיה, בעיות בחוש הטעם והריח,
- הזיות, תגובות פסיכוטיות עם סיכון למחשבות או מעשיים אובדניים.
- נפילה חדה בלחץ הדם
- חולשת שרירים -חשוב בעיקר לחולי מיאסטנה גרביס (myasthenia gravis – מחלה נדירה של מערכת העצבים).
- דלקת בכבד, הפרעה בתפקוד הכלייה ולעיתים אי ספיקת כלייה כתוצאה מתגובה אלרגית של הכלייה
- חום, כאב גרון והרגשת חולי שאינה חולפת ייתכן ונגרמים מירידה במספר תאי ~~לדורית~~ הדם הלבנים
- חום ותגובה אלרגית ראתית

**תופעות לוואי נוספות :**
- ירידה בכדוריות הדם האדומות (אנמיה) יכולה לגרום להצהבה או חיוורון של העור עקב פגיעה בתאי הדם האדומים וירידה במספרם של כל סוגי תאי הדם.

- תגובה מוגברת של המערכת החיסונית (רגישות יתר)
- הזעת יתר
- כאב, כולל כאב בגב, חזה וגפיים
- בעיות בתנועתיות כולל קשיים בהליכה.
- התקף פורפיריה בחולים עם פורפיריה( מחלה מטבולית נדירה)
- תגובה אלרגית דלקתית של כלי דם

**תופעות המחייבות התייחסות מיוחדת:**

**הפסק הטיפול ופנה לבית חולים מיד**
**נדיר ביותר** (תופעות שיכולות להופיע בפחות מחולה 1 מתוך 10,000 חולים)
- תגובה אלרגית חמורה שסימניה יכולים לכלול פריחה , בעיות נשימה או בליעה , התנפחות שפתיים פנים גרון או לשון

**הפסק הטיפול ופנה לרופא מיד**
**נדיר** (תופעות שיכולות להופיע בפחות מחולה 1 מתוך 1,000 חולים)
- שלשול מימי/דמי ייתכן ומלווה בהתכווציות בבטן וחום גבוה - יכול לרמז על בעיה חמורה במעיים
- כאב ודלקת בגידים , תתכן קריעת גידים
- התכווציות

**נדיר ביותר** (תופעות שיכולות להופיע בפחות מחולה 1 מתוך 10,000 חולים)
- תחושת צריבה, עקצוץ, כאב או הפרעות בתחושה .

**תופעות לוואי נוספות :**
- פריחה עורית חמורה שיכולה לכלול שלפוחיות או קילוף של העור מסביב לשפתיים, עיניים, פה, אף ואיברי המין.
- איבוד תאבון, הצהבת העור והעיניים, צבע שתן כהה, גירוד, רגישות בקיבה – יכול לרמז על בעיה בכבד.

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בכל מקרה שבו הינך מרגיש/ה תופעות לוואי שלא צויינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מיד.

<u>מינון</u>: מינון לפי הוראות הרופא בלבד אין לעבור על המנה המומלצת

<u>שים לב:</u>
יש לחכות פרק זמן של שעתיים לפחות לפני או לאחר נטילת טאבניק לנטילת התרופות הבאות:
מלחי ברזל (ניתנים לטיפול באנמיה), סותרי חומצה המכילים מגנזיום או אלומיניום (ניתנים לצרבות וכאבים בקיבה) או סוקראלפאט ( תרופה הניתנת להגנה של דופן הקיבה)

<u>אופן השימוש:</u>
אין ללעוס! לבלוע את התרופה עם כוס מים
ניתן ליטול את התרופה עם הארוחה או בכל זמן בין הארוחות
ניתן לחצות את הטבליה

**********
כיצד תוכל/' לסייע להצלחת הטיפול?
**********
עליך להשלים את הטיפול שהומלץ על-ידי הרופא
גם אם חל שיפור במצב בריאותך אין להפסיק הטיפול בתרופה ללא התייעצות עם רופא

<u>מנע הרעלה!</u>
תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל-ידי כך תמנע הרעלה.
אם נטלת מנת יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לחדר מיון של בית-חולים, והבא אריזת התרופה איתך.
<u>אל תגרום להקאה</u> ללא הוראה מפורשת מרופא!

תרופה זו נרשמה לטיפול במחלתך, בחולה אחר/ת, היא עלולה להזיק. אל תתן תרופה זו לקרוביך, שכניך או מכריך.

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אין ליטול תרופות בחושך! בדוק התווית והמנה בכל פעם שהינך נוטל תרופה. הרכב/י משקפיים אם הינך זקוק/ה להם.

אחסנה:
מתחת ל-C $30^0$
גם לפי תנאי האריזה/אחסנה המומלצים, תרופות נשמרות לתקופה מוגבלת בלבד. נא לשים לב לתאריך התפוגה של התכשיר! בכל מקרה של ספק, עליך להיוועץ ברוקח שסיפק לך את התרופה.
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טאבניק 500 מ"ג: 29963

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ט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו

עלון מאושר
5.11.

**Tavanic 250mg and 500mg tablets – Prescribing Information**

## 1. NAME OF THE MEDICINAL PRODUCT

Tavanic Tablets 500 mg film-coated tablet

Tavanic Tablets 250 mg film-coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Tavanic contains 500 mg of levofloxacin as active substance corresponding to 512.46 mg of levofloxacin hemihydrate.
Each film-coated tablet of Tavanic contains 250 mg of levofloxacin as active substance corresponding to 256.23 mg of levofloxacin hemihydrate.
For excipients, see 6.1

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

In adults with infections of mild or moderate severity, Tavanic tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute sinusitis
- Acute exacerbations of chronic bronchitis
- 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 tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

***Duration of treatment***

The duration of treatment varies according to the course of the disease with a maximum duration of treatment of 14 days (see table below). As with antibiotic therapy in general, administration of Tavanic 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.

***Method of administration***

Tavanic tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals. Tavanic tablets should be taken at least two hours before or after iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

***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)* | **Duration of treatment** |
|---|---|---|
| Acute sinusitis | 500 mg once daily | 10 - 14 days |
| Acute exacerbations of chronic bronchitis | 250 to 500 mg once daily | 7 - 10 days |
| Community-acquired pneumonia | 500 mg once or twice daily | 7 - 14 days |
| Complicated urinary tract infections including pyelonephritis | 250 mg once daily | 7 - 10 days |
| Skin and soft tissue infections | 250 mg once daily or 500 mg once or twice daily | 7 - 14 days |

***Special populations***

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

| | **Dose regimen** | | |
|---|---|---|---|
| | **250 mg/24 h** | **500 mg/24 h** | **500 mg/12 h** |
| **Creatinine clearance** | *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<br><br>(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***

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.(See section 4.4 QT interval prolongation).

***In children***

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

**4.3 Contraindications**

Tavanic tablets 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 Tavanic may not be the optimal therapy. Nosocomial infections due to *P. aeruginosa* may require combination therapy.

***Exacerbation of myasthenia gravis***

Fluoroquinolones, including Tavanic, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid Tavanic in patients with known history of myasthenia gravis

***Tendinitis and tendon rupture***

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. This undesirable effect may occur within 48 hours of starting of treatment and may be bilateral The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Tavanic. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Tavanic must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

***Clostridium difficile-associated disease***

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Tavanic tablets, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Tavanic tablets must be stopped immediately and patients should be treated with supportive measures ± specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

***Patients predisposed to seizures***

Tavanic tablets are contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous system lesions, concomitant treatment with 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, 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.

***Superinfection***

As with other antibiotics, the use of TAVANIC, 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.

***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.

***Hypoglycemia***

As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic 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***

Although photosensitisation is very rare with levofloxacin, 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 Tavanic 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).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
(See section 4.2 *Elderl*y, section 4.5, section 4.8, section 4.9).

***Peripheral neuropathy***

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving

fluoroquinolones, including levofloxacin, which can be rapid in its onset. 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.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Effect of other medicinal products on Tavanic**

***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 Tavanic 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 Tavanic tablet administration (see section 4.2). No interaction was found with calcium carbonate.

***Sucralfate***

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

***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 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). (See section 4.4 QT interval prolongation).

**Other forms of interactions**

***Meals***

There is no clinically relevant interaction with food. Tavanic 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, Tavanic tablets must not be used in pregnant women (see section 4.3 and 5.3).

***Lactation***

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, Tavanic tablets must not be used in breast-feeding women (see section 4.3 and 5.3).

**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 5000 patients and on extensive post marketing experience.
The adverse reactions are described according to the MedDRA system organ class below.
Frequencies 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.

**Infections and infestations**

Uncommon : Fungal infection (and proliferation of other resistant microorganisms)

**Blood and lymphatic system disorders**

Uncommon : Leukopenia, eosinophilia
Rare : Thrombocytopenia, neutropenia
Very rare : Agranulocytosis
Not Known : Pancytopenia, haemolytic anaemia

**Immune system disorders**

Very rare : Anaphylactic shock (see section 4.4)
Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose Not known : Hypersensitivity (see section 4.4)

**Metabolism and nutrition disorders**

Uncommon : Anorexia
Very rare : Hypoglycemia, particularly in diabetic patients (see section 4.4)

**Psychiatric disorders**

Uncommon : Insomnia, nervousness
Rare : Psychotic disorder, depression, confusional state, agitation, anxiety
Very rare : Psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4), hallucination

**Nervous system disorders**

Uncommon : Dizziness, headache, somnolence
Rare : Convulsion, tremor, paraesthesia
Very rare : sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia

**Eye disorders**

Very rare : Visual disturbance

**Ear and Labyrinth disorders**

Uncommon : Vertigo
Very rare : Hearing impaired
Not known : Tinnitus

**Cardiac disorders**

Rare : Tachycardia
Not Known : Electrocardiogram QT prolonged (see section 4.4 QT interval prolongation and section 4.9)

**Vascular disorders**

Rare : Hypotension

**Respiratory, thoracic and mediastinal disorders**

Rare : Bronchospasm, dyspnoea
Very rare : Pneumonitis allergic

**Gastrointestinal disorders**

Common : Diarrhoea, nausea
Uncommon : Vomiting, abdominal pain, dyspepsia, flatulence, constipation.
Rare : Diarrhoea –haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis

**Hepatobiliary disorders**

Common : Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon : Blood bilirubin increased
Very rare : Hepatitis
Not known: Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases (see section 4.4).

**Skin and subcutaneous tissue disorders**

Uncommon : Rash, pruritus
Rare : Urticaria
Very rare : Angioneurotic oedema, photosensitivity reaction
Not Known : Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis
Mucocutaneous reactions may sometimes occur even after the first dose

**Musculoskeletal and Connective tissue disorders**

Rare : Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), Arthralgia, Myalgia
Very rare : 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)
Not Known : Rhabdomyolysis

**Renal and urinary disorders**

Uncommon : Blood creatinine increased
Very rare : Renal failure acute (e.g. due to nephritis interstitial)

**General disorders and administration site conditions**

Uncommon : Asthenia
Very rare : Pyrexia
Not known : Pain (including pain in back, chest, and extremities)
Other undesirable effects which have been associated with fluoroquinolone administration include:
• 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 tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. 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

| | | | |
|---|---|---|---|
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| | | | |
| | | | |
| | | | |

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 (Cmax) 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.

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).

EUCAST clinical MIC breakpoints for levofloxacin (2006-06-20):

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Enterobacteriacae | ≤ 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*<br>*M.catarrhalis* [2] | ≤ 1 mg/L | >1 mg/L |
| Non-species related breakpoints[3] | ≤ 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 relate to high dose therapy.

[2] Strains with MIC values above the S/I 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 sent to a reference laboratory.

[3] 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)

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<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| Non Enterobacteriaceae. | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *Acinetobacter spp.* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *Stenotrophomonas maltophilia* | ≤ 2 µg/mL<br>≥ 17 mm | ≥ 8 µg/mL<br>≤ 13 mm |
| *Staphylococcus spp.* | ≤ 1 µg/mL<br>≥ 19 mm | ≥ 4 µg/mL<br>≤ 15 mm |

| | | |
|---|---|---|
| *Enterococcus spp.* | ≤ 2 µg/mL<br><br>≥ 17 mm | ≥ 8 µg/mL<br><br>≤ 13 mm |
| *H.influenzae*<br>*M.catarrhalis* [1] | ≤ 2 µg/mL<br><br>≥ 17 mm | |
| *Streptococcus pneumoniae* | ≤ 2 µg/mL<br><br>≥ 17 mm | ≥ 8 µg/mL<br><br>≤ 13 mm |
| *beta-hemolytic Streptococcus* | ≤ 2 µg/mL<br><br>≥ 17 mm | ≥ 8 µg/mL<br><br>≤ 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**

*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* * |
| *Morganella morganii* * |
| *Proteus mirabilis* * |
| *Providencia stuartii* |
| *Pseudomonas aeruginosa** |
| *Serratia marcescens* * |
| **Anaerobic bacteria** |
| *Bacteroides fragilis* |
| *Bacteroides ovatus$* |
| *Bacteroides thetaiotamicron$* |
| *Bacteroides vulgatus$* |
| *Clostridium difficile$* |

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

$ natural intermediate susceptibility

**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 h. The absolute bioavailability is approximately 100 %. Food has little effect on the absorption of levofloxacin.

**Distribution**

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

**Metabolism**

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

**Elimination**

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

**Subjects with renal insufficiency**

The pharmacokinetics of levofloxacin are 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:

| | | | |
|---|---|---|---|
| $Cl_{cr}$ [ml/min] | < 20 | 20 - 40 | 50 - 80 |
| $Cl_R$ [ml/min] | 13 | 26 | 57 |
| $t_{1/2}$ [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.

### Reproductive toxicity

Levofloxacin caused no impairment of fertility or reproductive performance in rats 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.
Levofloxacin had no effect on fertility and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

### 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. *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 photocarcinogenicity assay.

### 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 500 mg film-coated tablets** contain the following excipients for a weight of 630 mg:

***Tablet core:***

Crospovidone, hypromellose, microcrystalline cellulose and sodium stearyl fumarate.

***Tablet coating:***

Hypromellose, titanium dioxide (E 171), talc, macrogol 8000, yellow ferric oxide (E 172) and red ferric oxide (E 172).

**Tavanic 250 mg film-coated tablets** contain the following excipients for a weight of 315 mg:

***Tablet core:***

Crospovidone, hypromellose, microcrystalline cellulose and sodium stearyl fumarate.

***Tablet coating:***

Hypromellose, titanium dioxide (E 171), talc, macrogol 8000, yellow ferric oxide (E 172) and red ferric oxide (E 172).

### 6.2 Incompatibilities

Not applicable.

### 6.4 Special precautions for storage

Store below 30ºC

### 6.5 Nature and contents of container

PVC aluminium blisters containing film-coated tablets.

### 6.6 Special precautions for disposal and other handling

A score line allows adaptation of the dose in patients with impaired renal function.

## 7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel ltd.

## 8. MANUFACTURER

Sanofi Winthrop Industrie France ~~Sanofi-Aventis Germany~~