

TAVANIC® 500mg and 250mg tablets.

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו ביולי 2005

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tavanic 500mg tablets:

Each film-coated tablet of TAVANIC contains 500mg of levofloxacin as active ingredient corresponding to 512.46mg of levofloxacin hemihydrate.

Tavanic 250mg tablets:

Each film-coated tablet of TAVANIC contains 250mg of levofloxacin as active ingredient corresponding to 256.23mg of levofloxacin hemihydrate.

PHARMACEUTICAL FORM

Film-coated tablet.

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CLINICAL PARTICULARS**Therapeutic indications**

In adults with infections of mild to moderate severity TAVANIC tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible micro-organisms:

- Acute sinusitis,
- Acute exacerbation of chronic bronchitis,
- Community-acquired pneumonia,
- Complicated urinary tract infections including pyelonephritis,
- Skin and soft-tissue infections.

Consideration should be given to national and/or local guidance on the appropriate use of antibacterial agents.

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 therapy varies according to the course of the disease with a maximum duration of treatment of 14 days. 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 INTERACTIONS).

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	500mg once daily	10-14 days
Acute exacerbation of chronic bronchitis	250 to 500mg 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	250mg once daily or 500 mg once or	7-14 days

	twice daily	
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Dosage in patients with impaired renal function
(creatinine clearance \leq 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 (including hemodialysis and CAPD) *	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/24 h

* = No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Dosage in patients with 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.

Dosage in elderly

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

Contra-indications

TAVANIC tablets must not be used:

- in patients hypersensitive to levofloxacin, other quinolones or any of the excipients,
- in patients with epilepsy,
- in patients with history of tendon disorders following fluoroquinolone administration,
- in children or growing adolescents under 18 years old,
- during pregnancy,
- in breast-feeding women.

Special warnings and special 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.

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 halted immediately and patients should be treated with supportive measures \pm specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Tendinitis

Tendinitis, rarely observed with quinolones, may occasionally lead to rupture, involving the Achilles tendon in particular. This undesirable effect may occur within 48 hours of starting of treatment and may be bilateral. Elderly patients are more prone to tendinitis. The risk of tendon rupture may be increased by coadministration of corticosteroids. If tendinitis is suspected, treatment with TAVANIC tablets must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Patients predisposed to seizures

TAVANIC tablets are contra-indicated 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 INTERACTIONS).

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.

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.

Interactions with other medicaments and other forms of interaction

Iron salts, magnesium-or aluminum-containing antacids

Levofloxacin absorption is significantly reduced when iron salts, or magnesium-or aluminum-containing antacids are administered concomitantly with TAVANIC tablets. It is recommended that preparations containing divalent cations such as iron salts, or magnesium-or aluminum-containing antacids should not be taken 2 hours before or after TAVANIC tablet administration. 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.

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.

Cyclosporin

The half life of cyclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonist

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.

Meals

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

Other relevant information

Clinical pharmacology studies were carried out to investigate possible pharmacokinetic interactions between levofloxacin and some commonly prescribed drugs. 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, warfarin.

Use during pregnancy and lactation

Pregnancy

Reproductive studies in animals did not raise specific concerns. 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.

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.

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).

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 following frequency rating has been used:

very common - more than 10%
common - 1 to 10%
uncommon - 0.1 to 1%
rare - 0.01 to 0.1%
very rare - less than 0.01%
isolated cases

Allergic reactions

Uncommon: pruritus, rash,
Rare: urticaria, bronchospasm/dyspnoea,
Very rare: angio-oedema, hypotension, anaphylactic-like shock; photosensitisation
Isolated cases: severe bullous eruptions such as Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema exsudativum multiforme.

Muco-cutaneous, anaphylactic/-oid reactions may sometimes occur even after the first dose.

Gastro-intestinal, metabolism

Common: nausea, diarrhoea,
Uncommon: anorexia, vomiting, abdominal pain, dyspepsia,
Rare: bloody diarrhoea which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis,
Very rare: hypoglycaemia, particularly in diabetic patients.

Neurological

Uncommon: headache, dizziness/vertigo, drowsiness, insomnia,
Rare: depression, psychotic reactions (with e.g. hallucinations), paraesthesia, tremor, anxiety, agitation, confusion, convulsions,
Very rare: hypoaesthesia, visual and auditory disturbances, disturbances of taste and smell.,
Isolated cases: Psychotic reactions with self endangering behaviour including suicidal ideation or acts.

Cardiovascular

Rare: tachycardia, hypotension
Very rare: shock (anaphylactic/oid)
Isolated cases: QT-interval prolongation (see "overdose")

Musculo-skeletal

Rare: arthralgia, myalgia, tendon disorders including tendinitis (e.g. Achilles tendon),
Very rare: tendon rupture (e.g. Achilles tendon), as with other fluoroquinolones 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,
Isolated cases: rhabdomyolysis.

Liver, kidney

Common: increased liver enzyme levels (e.g. ALT, AST),
Uncommon: increase in bilirubin, increase in serum creatinine,
Very rare: liver reactions such as hepatitis ; acute kidney failure (e.g. due to interstitial nephritis)

Blood

Uncommon: eosinophilia, leukopenia,
Rare: neutropenia, thrombocytopenia,
Very rare: agranulocytosis,
Isolated cases: haemolytic anaemia, pancytopenia

Others

Uncommon: asthenia, fungal overgrowth and proliferation of other resistant microorganisms,
Very rare: allergic pneumonitis, fever.

Other undesirable effects which have been associated with fluoroquinolone administration include:

- psychotic reactions such as acute confusional states and depressive mood changes (these reactions may occur even after the first dose),
- extrapyramidal symptoms and other disorders of muscular coordination,
- hypersensitivity vasculitis,
- attacks of porphyria in patients with porphyria

Overdose

According to toxicity studies in animals, 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. Gastro-intestinal reactions such as nausea and mucosal erosions.

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

Management:

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

In case of acute oral overdose, gastric lavage should also be considered and 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class (ATC code J01MA) and is the S (-) enantiomer of the racemic drug substance ofloxacin.

Mode of action

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

Breakpoints

The preliminary NCCLS (US National Committee on Clinical Laboratory Standards) recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are: Susceptible ≤ 2 mg/L, resistant ≥ 8 mg/L

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. Therefore, the information presented provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to levofloxacin or not. Only microorganisms relevant to the given clinical indications are presented here.

SUSCEPTIBLE MICROORGANISMS

Aerobic Gram-positive

*Enterococcus faecalis**, *Staphylococcus aureus** methi-S, *Staphylococcus haemolyticus* methi-S, *Staphylococcus saprophyticus*, *Streptococci*, groups C and G, *Streptococcus agalactiae*, *Streptococcus pneumoniae** peni-I/S/R, *Streptococcus pyogenes**

Aerobic gram-negative

*Acinetobacter baumannii**, *Citrobacter freundii**, *Eikenella corrodens*, *Enterobacter aerogenes*, *Enterobacter agglomerans*, *Enterobacter cloacae**, *Escherichia coli**, *Haemophilus influenzae** ampi-S/R, *Haemophilus parainfluenzae**, *Klebsiella oxytoca*, *Klebsiella pneumoniae**, *Moraxella catarrhalis** β +/ β -, *Morganella morganii**, *Pasteurella multocida*, *Proteus mirabilis**, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa**, *Serratia marcescens**

Anaerobic

Bacteroides fragilis, *Clostridium perfringens*, *Peptostreptococcus*.

“Other“

*Chlamydia pneumoniae**, *Chlamydia psittaci*, *Legionella pneumophila**, *Mycoplasma pneumoniae**

* = clinical efficacy has been proven in clinical studies.

INTERMEDIATELY SUSCEPTIBLE MICROORGANISMS

Aerobic Gram-positive

Staphylococcus haemolyticus methi-R

Aerobic Gram-negative

Burkholderia cepacia

Anaerobic

Bacteroides ovatus, Bacteroides thetaiotamicron, Bacteroides vulgatus, Clostridium difficile.

RESISTANT MICROORGANISMS

Aerobic Gram-positive

Staphylococcus aureus methi-R

Other information

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

Acquired resistance with levofloxacin has recently been documented in 1997:

- S. pneumoniae France \leq 1%
- H. influenzae : rare.

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

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

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%. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg. 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 μ g/g and 10.8 μ g/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 μ g/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 μ g/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 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 ($t_{1/2}$ = 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.

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 kinetics 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.

Preclinical safety data

Acute toxicity

The median lethal dose (LD₅₀) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg. Administration of 500mg/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 reactions 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" (NOEL) in these studies were concluded to be 200 and 20 mg/kg/day after one-and six 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-months study. The NOELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.

The "No Observed Adverse Effect Levels" (NOEL) 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 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.

PHARMACEUTICAL PARTICULARS

List of excipients

TAVANIC 250mg and 500mg film-coated tablets contain the following excipients for a weight of 315 and 630mg respectively.

Tablet core

Crospovidone; methylhydroxypropylcellulose; microcrystalline cellulose and sodium stearyl fumarate.

Tablet coating

Methylhydroxypropylcellulose; titanium dioxide (E 171); talc; polyethylene glycol; yellow ferric oxide (E 172) and red ferric oxide (E 172).

Incompatibilities

Not applicable.

Shelf-life

60 months

Special precautions for storage

No special conditions for storage.

Nature and content of container

PVC aluminum blisters containing 1, 5, 7 and 10 film-coated tablets.

Instructions for use / handling

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

MANUFACTURER: Aventis Pharma, Germany

MANUFACTURER'S AGENT: Aventis Pharma Ltd., P.O.B. 8090, Netanya 42504

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