APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM)

TAVANIC 250 (tablets)

TAVANIC 500 (tablets)

TAVANIC I.V. 250 (ready for use solution for intravenous infusion)

TAVANIC I.V. 500 (ready for use solution for intravenous infusion)

COMPOSITION

TAVANIC 250: Each tablet contains levofloxacin hemihydrate equivalent to 250 mg levofloxacin.

TAVANIC 500: Each tablet contains levofloxacin hemihydrate equivalent to 500 mg levofloxacin.

Excipients: Each tablet also contains crospovidone, macrogol 8000, methylhydroxypropyl cellulose, microcrystalline cellulose, red ferric oxide, sodium stearylfumarate, talc, titanium dioxide and yellow ferric oxide.

TAVANIC I.V. 250: Each 50 ml vial of solution for infusion contains levofloxacin hemihydrate equivalent to 250 mg (5 mg per ml) levofloxacin.

TAVANIC I.V. 500: Each 100 ml vial of solution for infusion contains levofloxacin hemihydrate equivalent to 500 mg (5 mg per ml) levofloxacin.

Excipients: The solution also contains sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and Medium Spectrum Antibiotics

PHARMACOLOGICAL ACTION

Levofloxacin is a synthetic broad spectrum antibacterial fluoroquinolone which is the S (-) enantiomer (levorotatory form) of the racemic drug substance ofloxacin for oral and intravenous administration. Levofloxacin acts on the DNA-DNA-gyrase complex by inhibiting DNA-gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, transcription, repair and recombination, and topoisomerase IV. Levofloxacin is bactericidal *in vitro*. Its antibacterial spectrum covers many Gram-positive and Gram-negative bacteria.

Infections caused by the following organisms have been successfully treated with levofloxacin in clinical trials:

Gram positive organisms:

Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus faecalis.

Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis.

Gram negative organisms:

Acinetobacter calcoaceticus, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa, S. marcescens and *Enterobacter aerogenes.*

Other organisms:

Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae.

In vitro there is 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.

Pharmacokinetics:

Food has little effect on the absorption of levofloxacin and the tablets may be taken during or between meals. The absorption of levofloxacin is significantly reduced when administered with iron salts, antacids and sucralfate.

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within one hour. The absolute bioavailability is approximately 100 %. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.

Distribution:

Approximately 30 - 40 % of levofloxacin is bound to serum protein. Multiple doses of 500 mg once daily 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 three days.

Diffusion in fluids and tissues:

Levofloxacin diffuses well into bone tissue, bronchial mucosa, epithelial lining fluid, lung tissue and blister fluid.

Metabolism and Elimination:

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyllevofloxacin and levofloxacin N-oxide. Elimination of levofloxacin occurs primarily via the kidney. The elimination half-life ($t_{½}$) is on average six to eight hours in patients following oral and intravenous administration.

INDICATIONS

In adults, treatment of bacterial infections due to levofloxacin-susceptible micro-organisms:

Sinusitis due to *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis* and *H. parainfluenzae.*

Acute exacerbations of chronic bronchitis due to *H. influenzae, K. pneumoniae, S. aureus, M. catarrhalis, E. coli, H. parainfluenzae* and *S. pneumoniae.*

Community Acquired Pneumonia due to *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila.*

Chronic Bacterial Prostatitis due to *Eschericia coli*, *Enterrococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis.*

Complicated urinary tract infections and acute pyelonephritis due to *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae, P. aeruginosa.*

Uncomplicated urinary tract infections in women due to *E. coli.*

Uncomplicated skin and skin structure infections due to *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E. coli, K. pneumoniae, S. faecalis.*

Complicated skin and skin structure infections due to *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*.

Intra-abdominal infections due to *E. coli* and anaerobic micro-organisms.

CONTRAINDICATIONS

- Hypersensitivity to levofloxacin, other quinolones, or any of the excipients.
- Epilepsy.
- History of tendon disorders related to fluoroquinolone, including TAVANIC administration.
- Children or adolescents.
- Pregnancy and lactation (see Pregnancy and Lactation).

WARNINGS and SPECIAL PRECAUTIONS

TAVANIC should be used with 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.

TAVANIC SHOULD NOT BE GIVEN TO PATIENTS UNDER 18 YEARS OF AGE.

Even when used as instructed, TAVANIC may alter reactivity to such an extent that the ability to drive or operate machinery may be impaired.

Although photosensitisation is extremely rare with TAVANIC, 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.

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

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

Pseudomembranous colitis

Diarrhoea, particulary if severe, persistent and/or bloody, during or after treatment with TAVANIC, may be symptomatic of pseudomembranous colitis due to *Clostridium difficile.* If pseudomembranous colitis is suspected, TAVANIC must be stopped immediately.

Tendinitis

Tendinitis, which has been observed with quinolones, may occasionally lead to rupture involving 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 co-administration of corticosteroids. If tendinitis is suspected, treatment with TAVANIC must be halted immediately.

Disturbances in blood glucose, including both hyperglycemia and hypoglycemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic medicine or with insulin. Cases of hypoglycemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

QT-interval prolongation

Caution should be taken when using fluoroquinolones, including TAVANIC, in patients with known risk factors for prolongation of the QT-interval such as, for example:

- Elderly.
- Uncorrected electrolyte balance (e.g. hypokalaemia, hypomagnesaemia).
- Congenital long QT syndrome.
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).
- Concomitant use of medicines that are known to prolong QT-interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides). (see **INTERACTIONS**).

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including TAVANIC, which can be rapid in its onset, can be rapidly progressive and in some cases can be irreversible. TAVANIC should be discontinued if the patient experiences symptoms of neuropathy. This would minimise the possible risk of developing an irreversible condition.

INTERACTIONS

If mineral-containing antacids or iron preparations are taken at the same time, absorption of TAVANIC tablets may be impaired. 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.

The bioavailability of TAVANIC tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and TAVANIC tablets, it is best to administer sucralfate two hours after the TAVANIC tablet administration.

No pharmacokinetic interactions of TAVANIC were found with theophylline in a clinical study. However there are indications of a pronounced lowering of the cerebral seizure threshold when quinolones are given concurrently with other medicines that lower the seizure threshold (e.g. theophylline) or with fenbufen or similar non-steroidal anti-inflammatory drugs.

Caution should be exercised when TAVANIC is co-administered with medicines that affect the tubular renal secretion such as probenecid and cimetidine, especially in renal impaired patients.

Increased coagulation tests (PT/INR) and/or bleeding which may be severe, have been reported in patients treated with TAVANIC in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests should be monitored in patients treated with vitamin K antagonists.

TAVANIC, like other fluoroquinolones, should be used with caution in patients receiving medicines known to prolong the QT-interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides) (see **WARNINGS and SPECIAL PRECAUTIONS).**

PREGNANCY AND LACTATION

TAVANIC is conta-indicated during pregnancy and lactation because animal studies have shown that levofloxacin may affect joint development in growing organisms (See **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

TAVANIC tablets:

TAVANIC tablets should be swallowed whole, without crushing, and with sufficient amount of liquid. TAVANIC tablets may be taken on an empty stomach or with meals.

TAVANIC tablets should be taken two hours before iron salts, antacids and sucralfate administration since reduction of absorption may occur.

A score line allows for adaption of the dose in patients with renal impairment.

TAVANIC I.V. solution for infusion:

TAVANIC I.V. solution for infusion should be infused slowly over a period of not less than 30 minutes for a dosage of 250 mg. TAVANIC I.V. solution for infusion should be infused slowly over a period of not less than 60 minutes for a dosage of 500 mg. TAVANIC solution for infusion should be used within three hours after perforation of the rubber stopper in order to prevent any

bacterial contamination. No protection from light is necessary during infusion. TAVANIC solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate). If its compatibility with other infusion solutions has not been proven, TAVANIC I.V. should as a rule be applied separately.

TAVANIC I.V. is compatible with the following infusion solutions:

- 0,9 % sodium chloride solution USP (Isotonic saline solution),
- 5, 0 % dextrose injection, USP
- 2,5 % dextrose in ringer solution
- Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes)

It is usually possible to switch from initial intravenous treatment to the oral route after a few days, according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Dosage:

TAVANIC is administered once or twice daily.

The dosage depends on the type and severity of infection and sensitivity of the presumed causative pathogen. The duration of therapy varies according to the course of the disease. TAVANIC 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.

The following daily dose recommendations can be given for TAVANIC:

Recommended daily dosage in patients with normal renal function:

Sinusitis due to *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis* and *H. parainfluenzae*: 500 mg once daily for 10 days.

Acute exacerbation of chronic bronchitis due to *H. influenzae, K. pneumoniae, S. aureus, M. catarrhalis, E. coli, H. parainfluenzae* and *S. pneumoniae*: 500 mg once daily for 5 - 10 days.

Community Acquired Pneumonia due to *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis, H. parainfluenzae, K. pneumoniae, E. coli, Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila*: 500 mg once or twice daily for 10 - 14 days.
(The higher dosage should be chosen in the presence of complicating factors e.g. co-morbidity, advanced age).

Chronic Bacterial Prostatitis due to *Eschericia coli, Enterrococcus faecalis, Staphylococcus epidermidis, Staphylococcus haemolyticus, Streptococcus agalactiae, Streptococcus mitis*: 500 mg once a day for 28 days.

Complicated urinary tract infections and acute pyelonephritis due to *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae, P. aeruginosa*: 250 mg once daily for 10 days.

Uncomplicated urinary tract infections in women due to *E. coli*: 250 mg once daily for 3 days.

Uncomplicated skin and skin structure infections due to *S. aureus, S. pyogenes, Acinetobacter calcoaceticus, E. cloacae, P. mirabilis, P. aeruginosa, E.coli, K. pneumoniae, S. faecalis*: 250 to 500 mg once daily for 7 - 10 days.

Complicated skin and skin structure infections due to *S. aureus, S. pyogenes, P. mirabilis, E. coli, K. pneumoniae, S. faecalis, E. cloacae, K. oxytoca*: 500 mg twice daily for 10 - 14 days.

Intra-abdominal infections due to *E. coli* and anaerobic micro-organisms: 500 mg once daily in combination with an antibiotic with anaerobic coverage for 10 -14 days.

Above indications when bacteraemia or septicaemia is present: 500 mg twice daily for 10 - 14 days.

Recommended daily dosage in patients with impaired renal function:

Dosage must be adjusted in patients with impaired renal function (creatinine clearance ≤ 50 ml/min) according to the degree of impairment:

With a creatinine clearance between 20 and 50 ml/min:

In patients meant to be taking 250 or 500 mg once daily, a normal single dose should be given initially; and then reduced by half the dose once daily.

If the patient is meant to be taking 500 mg twice daily, the initial dose should be 500 mg and then 250 mg should be administered twelve hourly.

With a creatinine clearance between 10 and 19 ml/min:

In patients meant to be taking 250 mg once daily, a normal single dose should be given initially and then reduced to 125 mg every 48 hours. Patients meant to be taking 500 mg once daily should be given a normal single dose initially and then this dose should be reduced to 125 mg every 24 hours.

Patients meant to be taking 500 mg twice daily should be given 500 mg initially and then the dose should be reduced to 125 mg every 12 hours.

With a creatinine clearance of less than 10 ml/min or in patients on haemodialysis or CAPD (Continuous Ambulatory Peritoneal Dialysis):

If the prescribed dosage is 250 mg once daily, a normal single dose should be given initially and then this dose should be reduced to 125 mg every 48 hours. Patients meant to be taking 500 mg once daily should be given a normal single dose initially and then the dose should be reduced to 125 mg every 24 hours. Patients meant to be taking 500 mg twice daily should be given 500 mg initially and then the dose should be reduced to 125 mg every 24 hours.

No adjustment of dosage is required in the elderly or in patients with impaired liver function.

SIDE-EFFECTS

Adverse reactions have been ranked according to CIOMS recommendation and frequency rating as follows:

Very common: > 10 %; **Common:** 1 % to 10 %; **Uncommon:** 0.1 % to 1 %; **Rare:** 0.01 % to 0.1 %; **Very rare, including isolated reports:** < 0.01 %; **Not known**

Anaphylactic/oid reactions, skin reactions

Uncommon: Pruritus, rash

Rare: Urticaria

Very rare, including isolated reports: Angio-oedema, hypotension, anaphylactic/oid shock, photosensitisation

Severe bullous eruptions such as Steven's Johnson syndrome, toxic epidermal necrolysis (Lyells' syndrome) and erythema exsudativum multiforme

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

Metabolism and nutrition disorders

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.

Hypoglycaemia, particularly in diabetic patients (see **WARNINGS and SPECIAL PRECAUTIONS**).

Post-marketing adverse reactions: Hyperglycaemia, hypoglycaemic coma

Neurological/Psychiatric

Uncommon: Headache, dizziness/vertigo, drowsiness, insomnia

Rare: Depression, anxiety, psychotic reactions (with e.g. hallucinations), restlessness, paraesthesia, tremor, agitation**,** confusion, convulsions

Very rare, including isolated reports: Sensory or sensorimotor peripheral neuropathy (see **WARNINGS and SPECIAL PRECAUTIONS**), visual and auditory disturbances, disturbances of taste and smell.

Psychotic reactions with self-endangering behaviour including suicidal ideation or acts.

Cardiac disorders

Rare: Hypotension, tachycardia

Very rare, including isolated reports: Shock (anaphylactic/oid); QT-interval prolongation (see **WARNINGS and SPECIAL PRECAUTIONS**).

Musculo-skeletal, connective tissue and bone disorders

Rare: Arthralgia, myalgia, tendon disorders including tendinitis (e.g. Achilles tendon)

Very rare, including isolated reports: Tendon rupture (e.g. Achilles tendon), muscular weakness, which may be of special importance in patients with myasthenia gravis, Rhabdomyolysis.

Hepato-biliary

Common: Increase in liver enzymes (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)

Not known: Severe liver injury, including cases with acute liver failure, sometimes fatal, have been reported with TAVANIC, primarily in patients with severe underlying diseases (e.g. sepsis).

Blood and lymphatic system disorders

Uncommon: Eosinophilia, leukopenia

Rare: Neutropenia, thrombocytopenia

Very rare: Agranulocytosis

Isolated cases: Haemolytic anaemia, pancytopenia

Others

Common: ***applicable for infusion only:*** Local irritation, pain, reddening of the infusion site and phlebitis

Uncommon: Asthenia, fungal overgrowth and proliferation of other resistant micro-organisms

Very rare: Allergic pneumonitis, fever

Other possible undesirable effects related to the class of fluoroquinolones

Very rare: Hypersensitivity vasculitis, attacks of porphyria in patients with porphyria

Extrapyramidal symptoms and other disorders of muscular coordination.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

According to studies in animals, the most important signs to be expected following acute overdosage of TAVANIC 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 patients should be carefully observed (including ECG monitoring) and symptomatic treatment should be implemented.

In case of an acute oral overdose, gastric lavage should also be considered and antacids may be used for protection of gastic mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

IDENTIFICATION

TAVANIC 250 (tablets): Pale yellowish-white to reddish-white, oblong, biconvex film-coated tablets with a score line (13 x 6 mm).

TAVANIC 500 (tablets): Pale yellowish-white to reddish-white, oblong, biconvex film-coated tablets with a score line (16 x 7.6 mm).

TAVANIC I.V. 250 (solution for infusion): Greenish-yellow solution in clear, colourless glass vials with a blue tear-off lid.

TAVANIC I.V. 500 (solution for infusion): Greenish-yellow solution in clear, colourless glass vials with a blue tear-off lid.

PRESENTATION

TAVANIC 250 (tablets): A carton containing blister packs of 3 or 5 tablets.

TAVANIC 500 (tablets): A carton containing one or more blister packs of 5 tablets each or one blister of 10 tablets.

TAVANIC I.V. 250 (solution for infusion): 1 infusion vial of 50 ml per carton.

TAVANIC I.V. 500 (solution for infusion): 1 infusion vial of 100 ml per carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C in a dry place.

Protect from light. Keep in the pack until required.

Once the infusion vial has been opened, the infusion solution must be used within three hours, stored at 25 °C.

The infusion vial can be refrigerated at 2 °C to 8 °C.

Do not use later than the date of expiry.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

TAVANIC 250	32/20.1.1/0123
TAVANIC 500	32/20.1.1/0124
TAVANIC I.V. 250	34/20.1.1/0002
TAVANIC I.V. 500	32/20.1.1/0125

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION

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