INDICATIONS CONTRA-INDICATIONS DOSAGE SIDE-EFFECTS PREGNANCY OVERDOSE IDENTIFICATION PATIENT INFORMATION

TAVANIC

SCHEDULING STATUS:
S4

PROPRIETARY NAME
(and dosage form):

TAVANIC

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
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

PHARMACOLOGICAL CLASSIFICATION:
A 20.1.1 - Broad and Medium Spectrum Antibiotics

PHARMACOLOGICAL ACTION:
TAVANIC is a synthetic broad spectrum antibacterial fluoroquinolone containing levofloxacin 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.
TAVANIC 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 TAVANIC in clinical trials:
Gram positive organisms: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus faecalis*.
Gram negative organisms: *Acinetobacter calcoaceticus, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa*.
Other organisms: *Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae.*
In vitro there is cross-resistance between TAVANIC and other fluoroquinolones.
Due to the mechanism of action, there is generally no cross-resistance between TAVANIC and other classes of antibacterial agents.
Pharmacokinetics: Food has little effect on the absorption of TAVANIC and the tablets may be taken

during or between meals. The absorption of TAVANIC is significantly reduced when administered with iron salts, antacids and sucralfate.
Absorption: Orally administered TAVANIC is rapidly and almost completely absorbed with peak plasma concentrations being obtained within one hour. The absolute bioavailability is approximately 100%. TAVANIC obeys linear pharmacokinetics over a range of 50 to 600 mg.
Distribution: Approximately 30 - 40% of TAVANIC is bound to serum protein. Multiple doses of 500 mg once daily with TAVANIC showed negligible accumulation. There is modest but predictable accumulation of TAVANIC after doses of 500 mg twice daily. Steady-state is achieved within three days.
Diffusion in fluids and tissues: TAVANIC diffuses well into bone tissue, bronchial mucosa, epithelial lining fluid, lung tissue and blister fluid.
Metabolism and Elimination: TAVANIC is metabolised to a very small extent, the metabolites being desmethyllevofloxacin and levofloxacin N-oxide. Elimination of TAVANIC occurs primarily via the kidney. The elimination half-life (t½) 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 microorganisms:
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.*
Complicated urinary tract infections and acute pyelonephritis: due to *E. coli, K. pneumoniae, S. faecalis, P. mirabilis, Enterobacter cloacae, P. aeruginosa*.
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.

CONTRA-INDICATIONS:
- Hypersensitivity to levofloxacin, other quinolones, or any of the excipients
- Epilepsy
- History of tendon disorders related to fluoroquinolone administration
- Children or adolescents
- During pregnancy and lactation because animal studies have shown that levofloxacin may affect joint development in growing organisms.

WARNINGS:
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 nonsteroidal 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.

DOSAGE AND DIRECTIONS FOR USE:

TAVANIC tablets: TAVANIC tablets should be swallowed whole, without crushing, and with sufficient amount of liquid. They 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 adaptation 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% 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).
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 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 $\leq$ 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 this 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 this 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 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 this 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 AND SPECIAL PRECAUTIONS:

- Gastro-intestinal symptoms may occur (gastric or abdominal symptoms, loss of appetite, nausea, vomiting, diarrhoea). The onset of diarrhoea, particularly if severe, persistent and / or bloody, during or after treatment with TAVANIC, may less frequently indicate the appearance of pseudomembranous colitis. Suspicion of pseudomembranous colitis requires immediate cessation of administration and treatment with appropriate specific antibiotic therapy. Products inhibiting peristalsis are contra-indicated in this clinical situation.
- Disturbances of the nervous system, e.g. headaches, dizziness, sleep disturbances, unsteady gait and tremor (disturbances of muscular co-ordination), numbness and tingling in the limbs (parasthesiae; visual and auditory disturbances, disturbances of the senses of taste and smell, hallucinations, convulsions and psychotic reactions such as restlessness, agitation, anxiety, depression and confusion. In some cases, these reactions have occurred already after the first dose. In the event of such adverse reactions, TAVANIC must be discontinued immediately and the doctor informed.
- Changes in the blood picture (leukopenia, eosinophilia, neutropenia, agranulocytosis, thrombocytopenia, pancytopenia, haemolytic anaemia), hepatitis and transient increases in liver enzymes and/or bilirubin and in serum creatinine have been observed. Interstitial nephritis and acute kidney failure may also occur.
- With the administration of TAVANIC I.V., local irritation, pain and reddening at the injection site, and phlebitis have been observed.
- Allergic manifestation may occur, in particular hypersensitivity reactions of the skin such as pruritus, rash, urticaria and vasculitis. Isolated cases of severe bullous eruptions such as Stevens-Johnson syndrome. toxic epidermal necrolysis (Lyells syndrome) and erythema exsudativum multiforme have been reported. Photosensitivity reactions (skin reactions on exposure to strong sunlight and artificial UV rays) have been reported. There have been symptoms such as fever, allergic pneumonitis, angio-oedema, hypotension and anaphylactic-like shock. In the event of such reactions, TAVANIC should be discontinued immediately. Medical treatment (therapy for shock) is imperative.
- Tendinitis (e.g. Achilles tendon) is less frequently observed with quinolones and if it is suspected, treatment with TAVANIC must be halted immediately and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. Other musculoskeletal side effects such as arthralgia and myalgia have been less frequently observed and less frequent occurrences include:
  * tendon rupture (Achilles tendon) - 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 of rhabdomyolysis have been reported.
- Hypoglycaemia, especially in diabetics, may occur.
- Asthenia, fungal overgrowth and proliferation of other resistant micro-organisms may occur.
- Fluoroquinolones are known to possibly trigger attacks of porphyria in patients suffering from porphyria.

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 drugs that lower the seizure threshold (e.g. theophylline) or with fenbufen or similar non-steroidal anti-inflammatory drugs.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
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.
Apart from symptomatic and supportive treatment, no specific therapeutic recommendation can be made in cases of overdosage.

IDENTIFICATION:
Tablets (250 mg): Pale yellowish-white to reddish-white, oblong, biconvex film-coated tablets with a score line (13 x 6 mm).
Tablets (500 mg): Pale yellowish-white to reddish-white, oblong, biconvex film-coated tablets with a score line (16 x 7,6 mm).
Infusion (250 mg): Greenish-yellow solution, clear, colourless glass vials, with a blue tear-off lid.
Infusion (500 mg): Greenish-yellow solution, clear, colourless glass vials, with a blue tear-off lid.

PRESENTATION:
TAVANIC 250 (tablets): A carton containing one blister pack of 5 tablets.
TAVANIC 500 (tablets): A carton containing one or more blister packs of 5 tablets each.
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 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 NUMBER:

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 APPLICANT:
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