APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

TAVANIC I.V. 750 (Ready for use solution for intravenous infusion)

COMPOSITION:

Each 150 ml vial of solution for infusion contains levofloxacin hemihydrate equivalent to 750 mg (5 mg per ml) levofloxacin.

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 750 mg in clinical trials:

Gram-positive organisms:

Methicillin-sensitive *Staphylococcus aureus, Streptococcus pneumoniae.*

Gram-negative organisms:

Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis.

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:

Absorption:

The absolute bioavailability is approximately 99 %.

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being attained within one to two hours.

Levofloxacin obeys linear pharmacokinetics over a range of 50-1 000 mg. Steady state conditions are reached after approximately 48 hours following levofloxacin 750 mg once daily dosage. Multiple doses of 750 mg once daily showed negligible accumulation.

Distribution:

Levofloxacin is widely distributed into tissues and body fluids: skin, lungs including epithelial lining fluid and alveolar cells. Approximately 30-40 % of levofloxacin is bound to serum protein.

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 mild bacterial infections due to levofloxacin-susceptible micro-organisms:

- Acute bacterial sinusitis due to *H. influenzae, S. pneumoniae, S. aureus, M. catarrhalis* and *H. parainfluenzae.*
- Acute exacerbations of chronic bronchitis due to *H. influenzae,* methillin-sensitive *S. aureus, M. catarrhalis, H. parainfluenzae* and *S. pneumoniae.*
- Community acquired pneumonia due to *H. influenzae, S. pneumoniae, H. parainfluenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila.*
- Hospital acquired pneumonia due to *H. influenzae, S. pneumoniae,* and methicillin-sensitive *S. aureus*.

CONTRAINDICATIONS:

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

WARNINGS AND SPECIAL PRECAUTIONS:

TAVANIC I.V. 750 SHOULD NOT BE GIVEN TO PATIENTS UNDER 18 YEARS OF AGE.

TAVANIC I.V. 750 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.

Pseudomembranous colitis:

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with TAVANIC I.V. 750, may be symptomatic of pseudomembranous colitis due to *Clostridium difficile*. If pseudomembranous colitis is suspected, TAVANIC I.V. 750 must be stopped immediately.

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 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 I.V. 750 must be halted immediately.

Even when used as instructed, TAVANIC I.V. 750 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 I.V. 750, 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 I.V. 750 may inhibit the growth of *Mycobacterium tuberculosis*, and therefore may give false-negative results in the bacteriological diagnosis of tuberculosis.

Patients with renal impairment:

Since TAVANIC I.V. 750 is excreted mainly by the kidneys, the dose of TAVANIC I.V. 750 should be adjusted in patients with renal impairment.

Prevention of photosensitisation:

Although photosensitisation is extremely rare with TAVANIC I.V. 750, 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.

QT-interval prolongation:

Caution should be taken when using fluoroquinolones, including TAVANIC I.V. 750, in patients with known risk factors for prolongation of the QT-interval such as, for example:

- elderly
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- congenital long QT syndrome
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
  concomitant use of medicines that are known to prolong the QT-interval (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides).

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolones, like TAVANIC I.V. 750.

Hypoglycaemia:

As with all quinolones, hypoglycaemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended.

Peripheral neuropathy:

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including TAVANIC I.V. 750, which can be rapid in its onset. TAVANIC I.V.

750 should be discontinued if the patient experiences symptoms of neuropathy. This would minimise the possible risk of developing an irreversible condition.

TAVANIC I.V. 750 may inhibit the growth of *Mycobacterium tuberculosis*, and therefore may give false-negative results in the bacteriological diagnosis of tuberculosis.

Even when used as instructed, TAVANIC I.V. 750 may alter reactivity to such an extent that the ability to drive or operate machinery may be impaired.

In patients treated with TAVANIC I.V. 750, determination of opiates in urine may give false-positive results.

INTERACTIONS:

- **Theophylline, fenbufen or similar non-steroidal anti-inflammatory medicines:**

No pharmacokinetic interactions of TAVANIC I.V. 750 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 medicines or other agents which lower the seizure threshold.

- **Probenecid and cimetidine:**

Caution should be exercised when TAVANIC I.V. 750 is co-administered with medicines that affect the tubular renal secretion such as probenecid and cimetidine, especially in renal impaired patients.

- **Vitamin K antagonist:**

Increased coagulation tests (PT/INR) and/or bleeding which may be severe, has been reported in patients treated with TAVANIC I.V. 750 in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests should be monitored in patients treated with vitamin K antagonists.

- **Medicines known to prolong QT-interval:**

TAVANIC I.V. 750 should be used with caution in patients receiving medicines known to prolong the QT interval (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides) (see SPECIAL PRECAUTIONS).

PREGNANCY AND LACTATION:

TAVANIC I.V. 750 is contraindicated for use during pregnancy and lactation (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

TAVANIC I.V. 750 solution for infusion is only intended for slow intravenous infusion.
TAVANIC I.V. 750 solution for infusion should be infused slowly over a period of not less than 90 minutes for a dosage of 750 mg.
TAVANIC I.V. 750 solution for infusion should be used immediately after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

TAVANIC I.V. 750 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. 750 should as a rule be applied separately.

TAVANIC I.V. 750 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 I.V. 750 is administered intravenously once daily.

The following daily dose recommendations can be given for TAVANIC I.V. 750:

- Acute bacterial sinusitis due to *H. influenzae, S. pneumoniae S. aureus, M. catarrhalis* and *H. parainfluenzae*: 750 mg once daily for 5 days.
- Acute exacerbations of chronic bronchitis due to *H. influenzae,* methicillin-sensitive *S. aureus, M. catarrhalis, H. parainfluenzae* and *S. pneumoniae*: 750 mg once daily for 3-5 days.
- Community acquired pneumonia due to *H. influenzae, S. pneumoniae, H. parainfluenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila*: 750 mg once daily for 5 days.
- Hospital acquired pneumonia due to *H. influenzae, S. pneumoniae,* and methicillin-sensitive *S. aureus*: 750 mg once daily for 10 to 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 750 mg once daily, a normal single dose should be given initially; and then 750 mg should be administered every 48 hours.

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

In patients meant to be taking 750 mg once daily, a normal single dose should be given initially and then reduced to TAVANIC 500 mg every 48 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 750 mg once daily, a normal single dose should be given initially and then this dose should be reduced to TAVANIC 500 mg every 48 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 % and < 10 %; **Uncommon:** ≥ 0,1 % and < 1 %; **Rare:** ≥ 0,01 % and < 0,1 %; **Very rare:** < 0,01 %; **Not known**

Cardiac disorders:

Rare: tachycardia

Not known: electrocardiogram QT prolonged

Blood and lymphatic system disorders:

Uncommon: leukopenia, eosinophilia

Rare: neutropenia, thrombocytopenia

Not known: pancytopenia, agranulocytosis, haemolytic anaemia

Nervous system disorders:

Common: headache, dizziness, vertigo

Uncommon: somnolence, tremor, dysgeusia

Rare: paraesthesia, convulsion

Not known: peripheral sensory neuropathy, peripheral sensory motor neuropathy, parosmia

Eye disorders:

Rare: visual disturbance

Ear and labyrinth disorders:

Uncommon: vertigo

Not known: hearing impaired

Respiratory, thoracic and mediastinal disorders:

Uncommon: dyspnoea

Very rare: allergic pneumonitis

Not known: bronchospasm

Gastrointestinal disorders:

Common: diarrhoea, vomiting, nausea

Uncommon: abdominal pain, dyspepsia

Not known: diarrhoea haemorrhagic, which may be indicative of enterocolitis, including pseudomembranous colitis

Renal and urinary disorders:

Uncommon: blood creatinine increased

Rare: renal failure acute (e.g. due to nephritis interstitial)

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus, urticaria

Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction.

Mucocutaneous reactions may sometimes occur even after the first dose

Musculoskeletal and connective tissue disorders:

Uncommon: arthralgia, myalgia

Rare: tendon disorders including tendinitis (e.g. Achilles tendon), muscular weakness, which may be of special importance in patients with myasthenia gravis

Not known: rhabdomyolysis, tendon rupture (e.g. Achilles tendon)

Metabolism and nutrition disorders:

Uncommon: anorexia

Rare: hypoglycaemia, particularly in diabetic patients

Infections and infestations:

Uncommon: fungal infection, pathogen resistance

Very rare: fungal overgrowth and proliferation of other resistant micro-organisms

Vascular disorders:

Common: phlebitis

Rare: hypotension

General disorders and administration site conditions:

Common: infusion site reaction (pain, reddening)

Uncommon: asthenia

Rare: pyrexia

Very rare: disturbances of taste and smell, fever

Immune system disorders:

Rare: angioedema

Not known: anaphylactic shock, anaphylactoid shock

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

Hepato-biliary disorders:

Common: hepatic enzyme increased (e.g. ALT/AST)

Uncommon: blood bilirubin increased

Not known: severe liver injury, including cases with acute liver failure, have been reported with TAVANIC I.V. 750, primarily in patients with severe underlying diseases (e.g. sepsis), hepatitis

Psychiatric disorders:

Common: insomnia

Uncommon: anxiety, confusional state

Rare: psychotic disorder (with e.g. hallucination), depression, agitation

Not known: psychotic disorder with self-endangering behaviour including suicidal ideation or suicide attempt

Other possible undesirable effects related to the class of fluoroquinolones:

Very rare: extrapyramidal symptoms and other disorders of muscular coordination, hypersensitivity vasculitis, attacks of porphyria in patients with porphyria

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Signs and symptoms:

According to studies in animals, the most important signs to be expected following acute overdosage of TAVANIC I.V. 750 are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures.

CNS effects including confusional state, convulsions, hallucinations and tremor have been observed in post-marketing experience.

Gastrointestinal 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.

Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing TAVANIC I.V. 750 from the body. No specific antidote exists.

IDENTIFICATION:

Greenish-yellow solution. Solution is sterile and practically free from visible particles.

PRESENTATION:

150 ml clear, colourless, Type 1 glass vial closed with a grey chlorobutyl rubber stopper and a silver (not painted) aluminium seal with a blue tear-off lid, packed in a paperboard carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

Do not remove the vial from the carton until required for use.

Discard any unused solution in accordance with local requirements.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

43/20.1.1/0948

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