

## APPROVED PACKAGE INSERT

### PROPRIETARY NAME AND DOSAGE FORM

**TAVANIC 750** (Tablets)

**SCHEDULING STATUS:** S4

### COMPOSITION:

Each tablet contains levofloxacin hemihydrate equivalent to 750 mg levofloxacin.

Each tablet also contains crospovidone, hypromellose, macrogol 8 000, microcrystalline cellulose, red ferric oxide, sodium stearyl fumarate, talc, titanium dioxide and yellow ferric oxide.

### PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and Medium Spectrum Antibiotics

### PHARMACOLOGICAL ACTION:

#### Pharmacodynamic properties

Levofloxacin is a synthetic broad spectrum antibacterial fluoroquinolone, which is the S (-) enantiomer (levorotatory form) of the racemic 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.

### **Pharmacokinetic properties**

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:**

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 ( $t_{1/2}$ ) 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 microorganisms:

- 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*, methicillin-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*.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

## **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 750 SHOULD NOT BE GIVEN TO PATIENTS UNDER 18 YEARS OF AGE.

TAVANIC 750 MAY INHIBIT THE GROWTH OF *Mycobacterium tuberculosis*, AND THEREFORE MAY GIVE FALSE-NEGATIVE RESULTS IN THE BACTERIOLOGICAL DIAGNOSIS OF TUBERCULOSIS.

TAVANIC 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 medicines or with medicines 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 750, may be symptomatic of pseudomembranous colitis due to *Clostridium difficile*. If pseudomembranous colitis is suspected, TAVANIC 750 must be stopped immediately.

**Tendinitis:**

Tendinitis, which is observed with the use of quinolones, such as TAVANIC 750, may occasionally lead to tendon 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 750 must be halted immediately. Tendonitis/rupture may occur after several weeks after discontinuation of TAVANIC 750.

TAVANIC 750 may cause photosensitisation, therefore 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 this from happening.

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.

**Patients with renal impairment:**

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

**Prevention of photosensitisation:**

Although photosensitisation is rare with TAVANIC 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 750, in patients with known risk factors for prolongation of the QT-interval such as, for example:

- elderly
- uncorrected electrolyte imbalance (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 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 750.

**Peripheral neuropathy:**

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including TAVANIC 750, which can be rapid in its onset. TAVANIC 750 should be discontinued if the patient experiences symptoms of neuropathy. This would minimise the possible risk of developing an irreversible condition.

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

**Effect on ability to drive and use machines:**

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

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

**INTERACTIONS:**

▪ **Iron salts, magnesium- or aluminium-containing antacids:**

It is recommended that preparations containing divalent or trivalent cations such as iron salts, or magnesium- or aluminium-containing antacids should not be taken two hours before or after TAVANIC 750 tablet administration as absorption may be impaired.

▪ **Sucralfate:**

The bioavailability of TAVANIC 750 tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and TAVANIC 750 tablets, it is best to administer sucralfate two hours after the TAVANIC 750 tablet administration.

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

No pharmacokinetic interactions of TAVANIC 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 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 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 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 WARNING AND SPECIAL PRECAUTIONS).

**PREGNANCY AND LACTATION:**

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

**DOSAGE AND DIRECTIONS FOR USE:**

TAVANIC 750 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 750 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.

**Dosage:**

TAVANIC 750 oral is administered once daily.

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

- Acute bacterial sinusitis due to *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *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  $\leq$  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 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 intravenously 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 intravenously once daily, a normal single dose should be given initially and then this dose should be reduced to TAVANIC 500 mg every 48 hours. This cannot be achieved with this tablet formulation.

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:**  $\geq 10\%$ ; **Common:**  $\geq 1\%$  and  $< 10\%$ ; **Uncommon:**  $\geq 0,1\%$  and  $< 1\%$ ;

**Rare:**  $\geq 0,01\%$  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

**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

**Not known:** Hyperglycaemia, hypoglycaemic coma

**Infections and infestations:**

**Uncommon:** fungal infection, pathogen resistance

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

**Vascular disorders**

**Rare:** hypotension

**General disorders and administration site conditions:**

**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 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 overdose of TAVANIC 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. 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 TAVANIC 750 from the body. No specific antidote exists.

**IDENTIFICATION:**

Pink, oblong, biconvex film-coated tablets with a score line.

**PRESENTATION:**

The tablets are packed in a transparent, colourless PVC blister strip with a silver aluminium foil backing, containing either 3, 5, 10 or 14 tablets. The blister strips are packed in a printed outer carton.

**STORAGE INSTRUCTIONS:**

Store at or below 30 °C. Protect from light.

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

**KEEP OUT OF REACH OF CHILDREN.**

**REGISTRATION NUMBER:**

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**NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF**

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