Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tavanic 500mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of levofloxacin in the form of levofloxacin hemihydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated Tablet

Product imported from Italy
Oblong with a score line, pale yellowish-white to reddish-white film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults with infections of mild or moderate severity, Tavanic tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections)
- Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections)
- Community-acquired pneumonia
- Complicated urinary tract infections including pyelonephritis
- Chronic bacterial prostatitis.
- Skin and soft tissue infections.

Before prescribing Tavanic, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolones.

4.2 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 treatment varies according to the course of the disease (see table below). 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 section 4.5).*

Posology

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	500 mg once daily	10 - 14 days
Acute exacerbations of chronic bronchitis	250 to 500 mg 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
Chronic bacterial prostatitis.	500 mg once daily	28 days
Skin and soft tissue infections	250 mg once daily or 500 mg once or twice daily	7 - 14 days

Special populations

Impaired renal function (creatinine clearance ≤ 50ml/min)

	Dose regimen		
Creatinine clearance	**250 mg/24 h**	**500 mg/24 h**	**500 mg/12 h**
50-20 ml/min	*first dose:* 250 mg *then:* 125 mg/24 h	*first dose:* 500 mg *then*: 250 mg/24 h	*first dose:* 500 mg *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 haemodialysis and CAPD) [1]	*then:* 125 mg/48 h	*then*: 125 mg/24 h	*then*: 125 mg/24 h

[1] No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

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.

In the elderly
No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.*(See section 4.4 QT interval prolongation).*

In children
Tavanic is contraindicated in children and growing adolescents *(see section 4.3).*

4.3 Contraindications

Tavanic tablets must not be used:

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

4.4 Special warnings and 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.

Tendinitis and tendon rupture
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed Tavanic. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Tavanic must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

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

Patients predisposed to seizures
Tavanic tablets are contraindicated 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 section 4.5).* In case of convulsive seizures, treatment with levofloxacin should be discontinued.

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.

Patients with renal impairment
Since levofloxacin is excreted mainly by the kidneys, the dose of Tavanic should be adjusted in patients with renal impairment *(see section 4.2).*

Hypersensitivity reactions
Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Hypoglycemia
As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended. *(See section 4.8).*

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.

Patients treated with Vitamin K antagonists
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with Tavanic in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly *(see section 4.5).*

Psychotic reactions
Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour- sometimes after only a single dose of levofloxacin *(see section 4.8).* In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

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

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
  (See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

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

Hepatobiliary disorders
Cases of hepatic necrosis up to life threatening hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis *(see section 4.8).* Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Tavanic

Iron salts, magnesium- or aluminium-containing antacids
Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids are administered concomitantly with Tavanic tablets. 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 *(see section 4.2).* 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 *(see section 4.2).*

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.

Other relevant information
Clinical pharmacology studies have shown that 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.

Effect of Tavanic on other medicinal products

Ciclosporin
The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists
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 *(see section 4.4).*

Drugs known to prolong QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides). *(See section 4.4 QT interval prolongation).*

Other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproductive studies in animals did not raise specific concern. 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 *(see sections 4.3 and 5.3).*

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 *(see sections 4.3 and 5.3).*

4.7 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).

4.8 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 adverse reactions are described according to the MedDRA system organ class below.
Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, ≤1/100), rare (≥ 1/10000, ≤1/1000), very rare (≤ 1/10000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Uncommon : Fungal infection (and proliferation of other resistant microorganisms)

Blood and lymphatic system disorders
Uncommon : Leukopenia, eosinophilia
Rare : Thrombocytopenia, neutropenia
Very rare : Agranulocytosis
Not Known : Pancytopenia, haemolytic anaemia

Immune system disorders
Very rare : Anaphylactic shock *(see section 4.4)*
Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose
Not known : Hypersensitivity *(see section 4.4)*

Metabolism and nutrition disorders
Uncommon : Anorexia
Very rare : Hypoglycemia, particularly in diabetic patients *(see section 4.4)*

Psychiatric disorders
Uncommon : Insomnia, nervousness
Rare : Psychotic disorder, depression, confusional state, agitation, anxiety
Very rare : Psychotic reactions with self-endangering behaviour including suicidal ideation or acts *(see section 4.4)*, hallucination

Nervous system disorders
Uncommon : Dizziness, headache, somnolence
Rare : Convulsion, tremor, paraesthesia
Very rare : sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia

Eye disorders
Very rare : Visual disturbance

Ear and Labyrinth disorders
Uncommon : Vertigo
Very rare : Hearing impaired
Not known : Tinnitus

Cardiac disorders
Rare : Tachycardia
Not Known : Electrocardiogram QT prolonged *(see section 4.4 QT interval prolongation and section 4.9)*

Vascular disorders
Rare : Hypotension

Respiratory, thoracic and mediastinal disorders
Rare : Bronchospasm, dyspnoea
Very rare : Pneumonitis allergic

Gastrointestinal disorders
Common : Diarrhoea, nausea
Uncommon : Vomiting, abdominal pain, dyspepsia, flatulence, constipation.
Rare : Diarrhoea –haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis

Hepatobiliary disorders
Common : Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon : Blood bilirubin increased
Very rare : Hepatitis
Not known: Jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases *(see section 4.4).*

Skin and subcutaneous tissue disorders
Uncommon : Rash, pruritus
Rare : Urticaria
Very rare : Angioneurotic oedema, photosensitivity reaction
Not Known : Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis

Mucocutaneous reactions may sometimes occur even after the first dose

Musculoskeletal and Connective tissue disorders
Rare : Tendon disorder *(see section 4.4)* including tendinitis (e.g. Achilles tendon), Arthralgia, Myalgia
Very rare : Tendon rupture *(see section 4.4).* 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
Not Known : Rhabdomyolysis

Renal and urinary disorders
Uncommon : Blood creatinine increased
Very rare : Renal failure acute (e.g. due to nephritis interstitial)

General disorders and administration site conditions
Uncommon : Asthenia
Very rare : Pyrexia
Not known : Pain (including pain in back, chest, and extremities)

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

- extrapyramidal symptoms and other disorders of muscular coordination,
- hypersensitivity vasculitis,
- attacks of porphyria in patients with porphyria.

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, 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, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones
ATC code: J01MA12

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

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

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance
The main mechanism of resistance is due to a *gyr-A* mutation. *In vitro* there is a 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.

Breakpoints
The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

EUCAST clinical MIC breakpoints for levofloxacin (2006-06-20):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriacae	≤ 1 mg/L	>2 mg/L
Pseudomonas spp.	≤ 1 mg/L	>2 mg/L
Acinetobacter spp.	≤ 1 mg/L	>2 mg/L
Staphylococcus spp.	≤ 1 mg/L	>2 mg/L
S.pneumoniae [1]	≤ 2 mg/L	>2 mg/L
Streptococcus A,B,C,G	≤ 1 mg/L	>2 mg/L
H.influenzae *M.catarrhalis* [2]	≤ 1 mg/L	>1 mg/L
Non-species related breakpoints[3]	≤ 1 mg/L	>2 mg/L

[1] the S/I-breakpoint was increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints relate to high dose therapy.

[2] Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.

[3] Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and are not for use with species where susceptibility testing is not recommended or for which there is insufficient evidence that the species in question is a good target (Enterococcus, Neisseria, Gram negative anaerobes)

The CLSI (Clinical and Laboratory Standards Institute, formerly NCCLS) recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (µg/mL) or disc diffusion testing (zone diameter [mm] using a 5 µg levofloxacin disc).

CLSI recommended MIC and disc diffusion breakpoints for levofloxacin (M100-S17, 2007):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm
Non Enterobacteriaceae.	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm
Acinetobacter spp.	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm
Stenotrophomonas maltophilia	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm
Staphylococcus spp.	≤ 1 µg/mL	≥ 4 µg/mL
	≥ 19 mm	≤ 15 mm
Enterococcus spp.	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm
H.influenzae	≤ 2 µg/mL	
M.catarrhalis [1]	≥ 17 mm	
Streptococcus pneumoniae	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm
beta-hemolytic Streptococcus	≤ 2 µg/mL	≥ 8 µg/mL
	≥ 17 mm	≤ 13 mm

[1] The absence or rare occurrence of resistant strains precludes defining any results categories other than « susceptible ». for strains yielding results suggestive of a « nonsuceptible » category, organism identification and antimicrobial susceptibility test results should be confirmed by a reference laboratory using CLSI reference dilution method.

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive bacteria

Staphylococcus aureus* *methicillin-susceptible*
Staphylococcus saprophyticus
Streptococci, group C and G
Streptococcus agalactiae
*Streptococcus pneumoniae **
*Streptococcus pyogenes **

Aerobic Gram- negative bacteria

Burkholderia cepacia$
Eikenella corrodens
*Haemophilus influenzae **
*Haemophilus para-influenzae **
Klebsiella oxytoca
*Klebsiella pneumoniae **
*Moraxella catarrhalis **
Pasteurella multocida
Proteus vulgaris
Providencia rettgeri

Anaerobic bacteria

Peptostreptococcus

Other

Chlamydophila *pneumoniae**
Chlamydophila *psittaci*
Chlamydia trachomatis
*Legionella pneumophila**
*Mycoplasma pneumoniae**
Mycoplasma hominis
Ureaplasma urealyticum

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria

*Enterococcus faecalis**
Staphylococcus aureus methicillin-resistant
Coagulase negative *Staphylococcus spp*

Aerobic Gram- negative bacteria

*Acinetobacter baumannii **
*Citrobacter freundii **
Enterobacter aerogenes
Enterobacter agglomerans
*Enterobacter cloacae **
*Escherichia coli **
*Morganella morganii **
*Proteus mirabilis**
Providencia stuartii
*Pseudomonas aeruginosa**
*Serratia marcescens**

Anaerobic bacteria

Bacteroides fragilis

Bacteroides ovatus[$]
Bacteroides thetaiotamicron[$]
Bacteroides vulgatus[$]
Clostridium difficile[$]

∗ Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
[$] natural intermediate susceptibility
+ More than 50% of resistance

Other information
Nosocomial infections due to *P. aeruginosa* may require combination therapy.

5.2 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 %.

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 p.o. were 8.3 µg/g and 10.8 µg/ml respectively. These were reached approximately one hour after administration.

Penetration into Lung Tissue
Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 µg/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 µg/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.

Penetration into prostatic tissue

After administration of oral 500mg levofloxacin once a day for three days, the mean concentrations in prostatic tissue were 8.7 µg/g, 8.2 µg/g and 2.0 µg/g respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

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.

Biotransformation
Levofloxacin is metabolised to a very small extent, the metabolites being 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 ($t_{½}$: 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.

Linearity
Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.

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 pharmacokinetics 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.

5.3 Preclinical safety data

Acute toxicity
The median lethal dose (LD_{50}) values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg.

Administration of 500 mg/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 reaction 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 (NOELs) in these studies were concluded to be 200 and 20 mg/kg/day after 1 and 6 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-month study. The NOELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.

The NOELs 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 foetuses 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 cells *in vitro* at or above 100 ∝g/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 oral and intravenous 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tavanic 500 mg film-coated tablets contain the following excipients:

Tablet core:

Crospovidone
Hypromellose
Microcrystalline cellulose
Sodium stearyl fumarate.

Tablet coating:

Hypromellose
Titanium dioxide (E 171)
Talc
Macrogol
Yellow iron oxide (E 172)
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package.

6.5 Nature and contents of container

PVC/ Aluminium blisters containing film-coated tablets.
Pack size for 500 mg tablets: 5 film-coated tablets.

6.6 Special precautions for disposal and other handling

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

As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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HA4 0NU
UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/173/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th September 2012

10 DATE OF REVISION OF THE TEXT