WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB338 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg levofloxacin (as hemihydrate).

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Pink, capsule-shaped, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have 'L' and '2' debossed (stamped into) on one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB338 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

It is also indicated as monotherapy for the prevention of multidrug-resistant tuberculosis in persons at risk.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

The therapy should be initiated by a health care provider experienced in the management of tuberculosis infection.

Treatment of tuberculosis

The recommended weight-based daily dose is 15–20 mg/kg. Duration of treatment depends on the regimen selected. In practice, the following doses of [TB338 trade name] may be given:

Patient weight	***Number of tablets daily***	***Daily dose***
3 to less than 5 kg	0.2 tablets*	50 mg
5 to less than 10 kg	0.5 tablets†	125 mg
10 to less than 16 kg	1 tablet	250 mg
16 to less than 24 kg	1.5 tablets#	375 mg
24 to less than 30 kg	2 tablets	500 mg
30 to less than 46 kg	3 tablets	750 mg
46 to 70 kg or more	4 tablets	1000 mg

*Given as 2 mL of an extemporaneous preparation containing 1 tablet in 10 mL of water (see Section 6.6)
†Given as 5 mL of an extemporaneous preparation containing 1 tablet in 10 mL of water (see Section 6.6)
#Given as 1 tablet plus 5 mL of an extemporaneous preparation containing an additional tablet in 10 mL of water (see Section 6.6)

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

An alternative formulation that can be divided into equal halves along a break line may be preferred for doses involving half tablets.

Alternative formulations containing higher doses of levofloxacin should be considered for doses involving multiple tablets of [TB338 trade name], to reduce pill burden for the patient.

Preventive treatment of MDR-TB

The recommended dose for preventive treatment of MDR-TB is given in the table below according to body weight. The tablet(s) are to be taken daily for 6 months.

Recipient weight		***Number of tablets daily***	***Daily dose***
3 to less than 6 kg	*If less than 3 months of age*	0.25 tablets*	62.5 mg
	3 months or age or more	0.5 tablets†	125 mg
6 to less than 10 kg	*Less than 6 months of age*	0.5 tablet†	125 mg
	6 months or age or more	1 tablet	250 mg
10 to less than 15 kg		1 tablet	250 mg
15 to less than 25 kg		1.5 tablets#	375 mg
25 to less than 50 kg		2 tablets	500 mg
50 kg or more		3 tablets	750 mg

*Given as 2.5 mL of an extemporaneous preparation containing 1 tablet in 10 mL of water (see Section 6.6)
†Given as 5 mL of an extemporaneous preparation containing 1 tablet in 10 mL of water (see Section 6.6)
Given as 1 tablet plus 5 mL of an extemporaneous preparation containing an additional tablet in 10 mL of water (see Section 6.6)

An alternative formulation that can be divided into equal halves along a break line may be preferred for doses involving half tablets.

Alternative formulations containing higher doses of levofloxacin should be considered for doses involving multiple tablets of [TB338 trade name], to reduce pill burden for the patient.

Special populations

Renal impairment

For adult patients with an estimated creatinine clearance ≤ 30 mL/min, with or without haemodialysis, the dose should be reduced to 750–1000 mg given three times per week.

Dose recommendations for paediatric patients with renal impairment have not been established.

Hepatic impairment

No adjustment of dosage is required.

Elderly

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to levofloxacin and reduce its effectiveness.

The patient should take a missed dose if it was due fewer than 12 hours ago. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient vomits within 1 hour of taking [TB338 trade name], the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Method of administration

Oral use.

[TB338 trade name] should be swallowed whole with a sufficient amount of liquid. The tablets can be taken with food or between meals.

4.3 Contraindications

[TB338 trade name] is contraindicated:

- in patients with hypersensitivity to levofloxacin, other quinolones or to any of the excipients (see section 6.1)
- in patients with epilepsy
- in patients with history of tendon disorders related to fluoroquinolone administration

4.4 Special warnings and precautions for use

The use of levofloxacin should be **avoided in patients who have experienced serious adverse reactions in the past** when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with levofloxacin should only be started if there are no alternative treatment options and after careful benefit/risk assessment.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors (see section 4.8). [TB338 trade name] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their health care provider for advice.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiological studies report an increased risk of aortic aneurysm and dissection, sometimes complicated by rupture, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing for:

- both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis);
- aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome);
- heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

Patients should be advised to consult a physician in an emergency department in case of sudden abdominal, chest or back pain, acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. It may occur at any time during therapy and also several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in the elderly, in patients with renal insufficiency, in patients who have received solid organ transplants, in patients treated with higher daily doses (≥ 1,000 mg) of levofloxacin, and in patients treated simultaneously with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. Close monitoring of these patients is necessary if they are prescribed levofloxacin.

All patients should consult their health care provider if they experience symptoms of tendinitis such as painful swelling and inflammation. If tendinitis is suspected, treatment with levofloxacin must be halted immediately and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. Corticosteroids should not be used if signs of tendinopathy occur.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent or bloody, during or after treatment with levofloxacin, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis, which can be life-threatening. Therefore, it is important to consider this diagnosis in patients who present with severe diarrhoea during or after treatment with levofloxacin. If pseudomembranous colitis is suspected, levofloxacin must be stopped immediately and appropriate treatment initiated without delay (e.g. linezolid). Products inhibiting peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones can lower the epileptic threshold and can trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with caution in patients predisposed to seizures 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 manifest 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 levofloxacin 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.

Severe skin reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction syndrome with eosinophilia and systemic symptoms (DRESS) have been reported with levofloxacin (see section 4.8) which may be life-threatening or fatal. Patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In 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 light (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) or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (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:

- congenital long QT syndrome
- concomitant use of medicines that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics, methadone)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- preexisting cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Elderly patients and women may be more sensitive to QTc-prolonging medications, therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy resulting in paraesthesia, hypaesthesia, dysesthesia or weakness has been reported in patients receiving fluoroquinolones, which can be rapid in its onset. Patients under treatment with levofloxacin should be advised to inform their health care provider prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop, in order to prevent the development of a potentially irreversible condition.

Patients with myasthenia gravis

Levofloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated. Fluroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis.

Hepatobiliary disorders

Cases of hepatic necrosis, including 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 health care provider if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Acute pancreatitis

Acute pancreatitis may be observed in patients taking levofloxacin. Patients should be informed of the characteristic symptoms of acute pancreatitis. Patients experiencing nausea, malaise, abdominal discomfort, acute abdominal pain or vomiting should have a prompt medical evaluation. If acute pancreatitis is suspected, levofloxacin should be discontinued; if confirmed, levofloxacin should not be restarted. Caution should be exercised in patients with a history of pancreatitis (see section 4.8)

Blood disorders

Bone marrow failure including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia, or agranulocytosis may develop during treatment with levofloxacin (see Section 4.8). If any of these blood disorders is suspected, blood counts should be monitored. In case of abnormal results, discontinuation of treatment with levofloxacin should be considered.

Interference with laboratory tests

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Iron salts, magnesium- or aluminium-containing antacids, didanosine

Levofloxacin absorption is significantly reduced when iron salts, magnesium- or aluminium-containing antacids or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with [TB338 trade name]. Concurrent administration of fluoroquinolones with multivitamin preparations with zinc appears to reduce their oral absorption.

It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken within 2 hours before or after administration of [TB338 trade name]. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Corticosteroids

Co-administration with corticosteroids increases the risk of tendinitis and tendon rupture.

Sucralfate

The bioavailability of levofloxacin is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and [TB338 trade name], it is best to administer sucralfate at least 2 hours after administration of [TB338 trade name].

Theophylline

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.

NSAIDs

Co-administration with nonsteroidal anti-inflammatory drugs (NSAIDs) may potentiate the risk of central nervous system toxicity sometimes associated with fluoroquinolone use. The interaction has been reported most often with enoxacin. It may occur with other fluoroquinolones as well, but is poorly documented. Patients with a history of seizures may be at greater risk (see also section 4.4.).
Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Other relevant information

Clinical pharmacology studies have shown that levofloxacin pharmacokinetics were not affected to any clinically relevant degree when levofloxacin was co-administered with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Ciclosporin

The half-life of ciclosporin was increased by 33% when co-administered with levofloxacin.

Vitamin K antagonists

Increases in coagulation parameters (as measured e.g. by PT/INR) or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Therefore, coagulation parameters should be closely 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, antipsychotics, methadone). (See section 4.4 “QT interval prolongation”).

Drugs undergoing renal tubular secretion

Co-administration of high doses of quinolones with other medicines that undergo renal tubular secretion (e.g. probenecid, cimetidine, frusemide and methotrexate) can lead to impairment of excretion and an increase in serum levels of the quinolone.

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

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

Pregnancy should be avoided in women treated with levofloxacin. Adequate contraceptive measures should be taken.

Pregnancy

There are limited data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However, in the absence of human data and due to experimental data suggesting a risk of damage to the weight-bearing cartilage of the growing organism by fluoroquinolones, levofloxacin should only be used in pregnancy if the benefit is considered to outweigh the risks, and there are no available treatment alternatives.

Breastfeeding

There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to experimental data suggesting a risk of damage to the weight-bearing cartilage of the growing organism by fluoroquinolones, [TB338 trade name] should be avoided during breastfeeding (section 5.3).

Fertility

No human data on the effect of [TB338 trade name] on fertility are available. Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

No studies on the effects of levofloxacin on the ability to drive and use machines have been performed. 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

Adverse events considered at least possibly related to levofloxacin treatment are listed below by body system, organ class and frequency. Frequency estimates are in many cases not based on adequately sized randomised trials, but on published data generated during post-approval use. Sometimes, no frequency data can be given. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to <1/1000), very rare (<1/10000), 'not known' (frequency cannot be estimated from the available data). Note that the frequencies relate to short-term therapy (<1 month).

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from available data)**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and lymphatic system disorders		Leucopenia Eosinophilia	Thrombocytopenia Neutropenia	Aplastic anaemia Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)	Anaphylactic shock [a] Anaphylactoid shock[a] (see section 4.4)

Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients Hypoglycaemic coma (see section 4.4)	Hyperglycaemia (see section 4.4),
Psychiatric disorders*	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams, nightmares Delirium	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4) Mania
Nervous system disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion (see sections 4.3 and 4.4) Paraesthesia Memory impairment	Peripheral sensory or sensorimotor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension Myoclonus
Eye disorders*			Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4) Uveitis
Ear and Labyrinth disorders*		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation) Electrocardiogram QT prolonged (see sections 4.4 and 4.9)

Vascular disorders**			Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Allergic pneumonitis
Gastro- intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis (see section 4.4)
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders [b]		Rash Pruritus Urticaria Hyperhidrosis	Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4) Fixed drug eruption	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis Skin hyperpigmentation
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Acute renal failure (e.g. due to interstitial nephritis)	
General disorders and administration site conditions*		Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

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

[b] Mucocutaneous reactions may sometimes occur even after the first dose

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Other undesirable effects which have been associated with fluoroquinolone administration include attacks of porphyria in patients with porphyria.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

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 [TB338 trade name] 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.

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

Treatment

There is no specific antidote. 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, peritoneal dialysis and CAPD are not effective in removing levofloxacin from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, fluoroquinolone. 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

Levofloxacin has *in vitro* activity against *M. tuberculosis*, as well as against a wide range of Gram-positive and Gram-negative pathogens. The bactericidal action of levofloxacin against *M. tuberculosis* results from the inhibition of the DNA gyrase, encoded by the *gyrA* and *gyrB* genes.

The wild-type levofloxacin MIC distribution for clinical isolates of *M. tuberculosis* has been reported by different investigators to range between 0.125-0.5 mg/L. When resistance to fluoroquinolones arises, it is generally caused by mutations in *gyrA.* Cross-resistance within the fluoroquinolone drug class is extensive, though not universal.

Clinical efficacy

Levofloxacin has been shown in clinical trials to be effective for the treatment and prevention of MDR-TB.

5.2 Pharmacokinetic properties

Pharmacokinetics of levofloxacin

General	
	Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 hours
Absorption	
Absolute bioavailability	Almost 100%
Oral bioavailability	Almost 100%
Food effect	No clinically relevant food effect
Distribution	
Volume of distribution (mean)	74 to 112 L
Plasma protein binding *in vitro*	24 – 38% bound to serum protein
Tissue distribution	Lung concentration: 2.4 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose (2- to 5-fold higher than plasma concentrations). Poor penetration into cerebro-spinal fluid. Levofloxacin has been shown to penetrate bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (bulla fluid) and prostate tissue.
Metabolism	
	Metabolized to a very small extent Metabolites: desmethyl-levofloxacin and levofloxacin N-oxide account for < 5% of the dose and are excreted in urine
Active metabolite(s)	None
Elimination	
Elimination half life	6 – 8 hours
Mean systemic clearance (Cl/F)	Mean apparent total body clearance approximately 144 to 226 mL/min Renal clearance approximately 96 to 142 mL/min
% of dose excreted in urine	> 85%
% of dose excreted in faeces	< 4%
Pharmacokinetic linearity	Linear over the 50 – 1000 mg dose range.
Drug interactions *(in vitro*)	
Transporters	No substrate or inhibitor.
Enzymes	No substrate or inhibitor.

Pharmacokinetics in special populations

Gender and race

No clinically relevant pharmacokinetic differences due to gender or race have been identified.

Elderly

There are no significant differences in levofloxacin kinetics between young and elderly subjects, **except those** associated with differences in creatinine clearance.

Renal impairment

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 – 49	50 – 80
Cl_R (mL/min)	13	26	57
$t_{1/2}$ (h)	35	27	9

Hepatic impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Paediatric population

Paediatric patients cleared levofloxacin faster than adult patients resulting in lower plasma exposures than adults for a given mg/kg dose.

5.3 Preclinical safety data

General toxicity

As with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

Non-clinical data reveal no other special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Mutagenicity/carcinogenicity

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential. Studies in the mouse 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 photocarcinogenity study.

Reproductive toxicity

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: microcrystalline cellulose
crospovidone
hydroxypropyl methylcellulose
magnesium stearate

Film coat: hypromellose

titanium dioxide

propylene glycol

talc

iron oxide red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container

Bottle pack

Opaque white plastic (HDPE) bottle containing 50 tablets. It also contains wadding to keep the tablets in place. The bottle has an opaque white, childproof plastic (polypropylene) screw cap with a sealing liner.

Blister pack

Clear colourless plastic (PVC) on aluminium foil blister cards, each containing 10 tablets. Available in packs of 1 x 10 or 10 x 10 tablets.

6.6 Special precautions for disposal and other handling

No special precautions

Preparation and administration - extemporaneous formulation for children

How to give [TB338 trade name]

If this medicine has been selected for a child weighing less than 10 kg, the responsible caregiver should be instructed how to make up a mixture with a [TB338 trade name] tablet and some water, as below.

You will need:

- 1 tablet of [TB338 trade name]
- drinking water
- a 10-mL oral syringe
- a container such as a bowl or a cup

1. Use the oral syringe to measure 10 mL drinking water into the container
2. Add 1 tablet of [TB338 trade name] and stir gently until the tablet breaks down and is fully mixed with the water. Make sure that the tablet breaks down completely
3. Use the oral syringe to give the right amount of the mixture:

For treatment of tuberculosis

Patient weight	***How much to give***
Child weighing **3 to less than 5 kg**	give **2 mL** of the mixture
Child weighing **5 to less than 10 kg**	give **5 mL** of the mixture (child may be given half a tablet instead of making up mixture, if they are able to swallow tablets)

For prevention of tuberculosis

Patient weight	***Age of child***	***How much to give***
3 to less than 6 kg	*If less than 3 months of age*	give **2.5 mL** of the mixture
	3 months of age or more	give **5 mL** of the mixture
6 to less than 10 kg	*If less than 6 months of age*	give **5 mL** of the mixture
	6 months of age or more	Child may be given **1 tablet daily** instead of a mixture

4. Throw away any mixture remaining in the bowl.

Repeat these steps every time you need to give the medicine.

If a formulation with a break line is not available and this medicine has been selected for a child weighing 16 to less than 24 kg (for treatment) or 15 to less than 25 kg (for prevention), the responsible caregiver should be instructed how to give a dose of 1.5 tablets, which involves taking a tablet supplemented with a mixture prepared from a [TB338 trade name] tablet and some water, as below.

You will need:

- 2 tablets of [TB338 trade name]
- drinking water
- a 10-mL oral syringe
- a container such as a bowl or a cup

1. Use the oral syringe to measure 10 mL drinking water into the container
2. Add 1 tablet of [TB338 trade name] and stir gently until the tablet breaks down and is fully mixed with the water. Make sure that the tablet breaks down completely
3. Use the oral syringe to measure 5 mL of the mixture, and give it to the child to take.
4. Then give the other tablet to the child to take, with enough drinking water to wash it down.
5. Throw away the rest of the mixture and wash the container.

Repeat these steps every time you need to give the medicine.

7. SUPPLIER

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products