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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB315 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink coloured, capsule shaped, biconvex, film coated tablet marked with "80" on one side and 'I' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB315 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

[TB315 trade name] is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

Consideration should be given to official treatment guidelines and recommendations for tuberculosis. Official guidance will normally include WHO and local health authorities' guidance.

4.2 Posology and method of administration

Posology

Adults, adolescents and children weighing at least 30 kg, and above 15 years of age:

The recommended dose is one 400 mg tablet once daily.

A higher dose may be used in certain MDR/RR-TB regimens. Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level fluoroquinolone resistance.

Dosing recommendations for high dose moxifloxacin treatment

Body weight	Number of 400-mg tablets	Daily dose
30 to less than 36 kg	1 or 1.5*	400–600 mg
36 to less than 46 kg	1.5*	600 mg
46 to less than 56 kg	1.5* or 2	600–800 mg
56 kg and over	2	800 mg

*Fractioning of tablets into halves is not possible with [TB315 trade name] since it is not scored, and an alternative formulation should be sought.

Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure, respectively.

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

***Children weighing less than 30 kg and under 15 years of age*:**

The recommended daily dose in children is 10 to 15 mg/kg bodyweight. The dose should be restricted to 10 mg/kg in those less than 6 months old.

Children weighing 24 to 30 kg may be given one 400-mg tablet of [TB315 trade name] daily.

Children weighing less than 24 kg should be given other formulations, e.g. dispersible tablets containing 100 mg moxifloxacin. If such formulations are not available, an extemporaneous formulation may be prepared from a moxifloxacin 400-mg tablet in 10 mL of water to achieve the following doses:

Child's weight	**Volume of extemporaneous formulation**	**Daily dose[+]**
5 to less than 7 kg	2 mL	80 mg
7 to less than 10 kg	3 mL	120 mg
10 to less than 16 kg	5 mL	200 mg
16 to less than 24 kg	5 mL to 7.5 mL	200–300 mg
24 kg and over	*(Use tablet)*	*400 mg (1 tablet)*

[+] Dispersing the tablet in water may facilitate administration in patients in lower weight-bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).

For detailed instructions on preparing such a formulation, see section 6.6 below: "Preparation and administration, extemporaneous formulation for children.

Renal impairment

No adjustment of dosage is required in patients with impaired renal function or in patients on chronic dialysis, including haemodialysis and continuous ambulatory peritoneal dialysis (see section 5.2).

Hepatic impairment

No dosage adjustment is recommended in hepatic impairment (see also section 4.4).

Elderly

No dosage adjustment is required in the elderly.

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 [TB315 trade name] 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 [TB315 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

[TB315 trade name] should be swallowed whole with sufficient liquid, and may be taken with food or between meals.

4.3 Contraindications

[TB315 trade name] is contraindicated in:

- Patients with hypersensitivity to moxifloxacin, other quinolones or to any of the excipients listed in section 6.1.
- Patients with a history of tendon disease/disorder related to quinolone treatment

- Patients with transaminase increase >5 fold ULN

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation. For reasons of drug safety, moxifloxacin is therefore contraindicated in patients with:

- Known QT prolongation (congenital or acquired)
- Electrolyte disturbances, particularly uncorrected hypokalaemia
- Clinically relevant bradycardia
- Clinically relevant heart failure with reduced left-ventricular ejection fraction
- History of symptomatic arrhythmias

4.4 Special warnings and precautions for use

The use of moxifloxacin 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 moxifloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions

Moxifloxacin has been shown to prolong the QTc interval on the electrocardiogram in some patients. In the analysis of ECGs obtained in the clinical trial program, QTc prolongation with moxifloxacin was 6 msec ± 26 msec, 1.4% compared to baseline. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Other drugs that prolong the QT interval (see also section 4.5) should be used only when strictly needed and with caution in patients receiving moxifloxacin. High dose therapy with moxifloxacin should be avoided. ECGs and serum potassium levels should be closely monitored.

Medication that can reduce potassium levels should be used with caution in patients receiving moxifloxacin (see also sections 4.3 and 4.5).

Moxifloxacin should be used with caution in patients who are taking medications associated with clinically significant bradycardia (see also section 4.3).

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest (see also section 4.3). The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.

If signs or symptoms of cardiac arrhythmia occur during treatment with moxifloxacin, treatment should be stopped and an ECG should be performed.

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. Moxifloxacin 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.

Hypersensitivity / allergic reactions

Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration. In these cases moxifloxacin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin (see section 4.8). Patients should be advised to contact their health care provider prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.

Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Patients with pre-existing impaired liver function

No dosage adjustment is recommended for mild, moderate, or severe hepatic insufficiency. However, some changes in the metabolism of moxifloxacin were observed in patients with hepatic insufficiency. Therefore, moxifloxacin should be used with caution in these patients.

Serious bullous skin reactions

Cases of severe or life-threatening skin reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis or acute generalised exanthematous pustulosis (AGEP) have been reported with moxifloxacin. Patients should be advised to contact their health care provider immediately if skin or mucosal reactions occur, before continuing treatment.

Patients predisposed to seizures

Quinolones are known to trigger seizures. They should be used with caution in patients with CNS disorders or in the presence of other risk factors which may predispose to seizures or lower the seizure threshold. In case of seizures, treatment with moxifloxacin should be discontinued and appropriate measures instituted.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including moxifloxacin. Patients receiving moxifloxacin 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 an irreversible condition.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-endangering behaviour such as suicide attempts. In the event that the patient develops these reactions, moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if moxifloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Antibiotic-associated diarrhoea including colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridioides difficile*-associated diarrhoea, have been reported in association with the use of broad spectrum antibiotics including moxifloxacin and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of moxifloxacin. If AAD or AAC is suspected or confirmed, ongoing treatment with antibacterial agents, including moxifloxacin, should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Medicines inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Patients with myasthenia gravis

Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Tendinitis, tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and may occur even several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in

older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) treatment with moxifloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Aortic aneurysm and dissection and heart-valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection and of aortic or mitral valve regurgitation or incompetence after intake of fluoroquinolones, particularly in the older population. 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 disease, or in patients diagnosed with pre-existing aortic aneurysm or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing for these conditions (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, rheumatoid arthritis, atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a health care provider in an emergency department. Patients should also be advised to seek immediate medical attention if they develop acute dyspnoea, new onset of heart palpitations, or oedema of the abdomen or lower extremities.

Patients with pre-existing renal disorders

Elderly patients with renal disorders should use moxifloxacin with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with moxifloxacin. In moxifloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitivity reactions

Quinolones have been shown to cause photosensitivity reactions in patients. However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Nevertheless patients should be advised to avoid exposure to UV irradiation or extensive/strong sunlight during treatment with moxifloxacin.

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones. Therefore, moxifloxacin should be used with caution in these patients.

Paediatric population

Due to adverse effects on the cartilage in juvenile animals (see section 5.3), and to limited documentation of the safety, moxifloxacin should only be used in children and adolescents with *M. tuberculosis* infection if the benefit is considered to exceed the risk and there are no treatment alternatives.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 mediated interactions

In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes. Also, CYP450 isoenzymes are not known to be

involved in the metabolism of moxifloxacin. Considering these results, metabolic interactions via cytochrome P450 enzymes are unlikely.

Clinical studies have shown that there are **no** interactions following concomitant administration of moxifloxacin with *ranitidine, probenecid, oral contraceptives, calcium supplements, morphine administered parenterally, theophylline, ciclosporin* or *itraconazole*.

Rifampicin

When co-administered with multiple doses of rifampicin, moxifloxacin AUC decreases by approximately 30%. The clinical consequences of this are unknown, and no dose adjustment is recommended on co-administration.

Rifapentine

When co-administered with multiple doses of rifapentine, moxifloxacin AUC decreased by 17%. The clinical consequences of this are unknown, and no dose adjustment is recommended on co-administration.

Rifabutin

No data are available on the effect of co-administration on the exposure to moxifloxacin and rifabutin.

QT-prolonging agents

An additive effect on QT interval prolongation of moxifloxacin and other agents that prolong the QT interval cannot be excluded. This effect might lead to an increased risk of ventricular arrhythmias, notably torsade de pointes. Therefore moxifloxacin should be used with caution in patients treated with any of the following drugs (see also section 4.4):

- antiarrhythmics class IA (e.g. *quinidine, hydroquinidine, disopyramide*),

- antiarrhythmics class III (e.g. *amiodarone, sotalol, dofetilide, ibutilide*),

- antipyschotics (e.g. *phenothiazines, pimozide, sertindole, haloperidol, sultopride*),

- tricyclic antidepressants (e.g. *amitriptyline, clomipramine, doxepin, imipramine, nortriptyline*),

- certain antimicrobial agents (*saquinavir, sparfloxacin, erythromycin (intravenous), pentamidine, antimalarials*, particularly *halofantrine*),

- certain antihistamines (*terfenadine, astemizole, mizolastine*),

- others (e.g. *cisapride*, intravenous *vincamine, bepridil, diphemanil*).

Potassium lowering agents

Moxifloxacin should be used with caution in patients who are taking medication that can reduce potassium levels (e.g. loop and thiazide-type diuretics, laxatives and enemas [high doses], corticosteroids, amphotericin B) or medication that is associated with clinically significant bradycardia.

Concomitant use with corticosteroids may also increase the risk of tendon disorders (see section 4.4).

Bivalent and trivalent cations

Formation of chelates with iron, aluminium and magnesium may inhibit the absorption of moxifloxacin. Taking agents containing these cations at the same time as, or close to, the intake of moxifloxacin may decrease moxifloxacin exposure by 25-60%. An interval of at least 6 hours should be left between administration of agents containing bivalent or trivalent cations (e.g. antacids containing *magnesium* or *aluminium*, *didanosine* tablets, *sucralfate* and agents containing *iron* or *zinc*) and administration of moxifloxacin.

Concomitant administration of *charcoal* with an oral dose of 400mg moxifloxacin led to a pronounced prevention of drug absorption and a reduced systemic availability of the drug by more than 80%. Therefore, the concomitant use of these two drugs is not recommended (except for overdose cases, see also section 4.9).

Glibenclamide

In studies conducted in diabetic volunteers, concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of approximately 21% in the peak plasma concentrations of

glibenclamide. However, the observed pharmacokinetic changes for glibenclamide did not result in any clinically relevant changes of the pharmacodynamic parameters (blood glucose, insulin).

Changes in INR

A large number of cases showing an increase in oral *anticoagulant* activity have been reported in patients receiving antibiotics, especially fluoroquinolones, macrolides, tetracyclines, cotrimoxazole and some cephalosporins. The infectious and inflammatory conditions, age and general status of the patient appear to be risk factors. Under these circumstances, it is difficult to evaluate whether the infection or the antibiotic therapy caused the INR (international normalised ratio) disorder. A precautionary measure would be to more frequently monitor the INR in patients on *warfarin* or any similar anticoagulants.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

The safety of moxifloxacin in human pregnancy has not been investigated. Moxifloxacin should only be used in pregnancy if the benefit is considered to outweigh the risks, and there are no available treatment alternatives. Reversible joint injuries are described in children receiving some quinolones; however this effect has not been reported as occurring on exposed foetuses. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pregnancy should be avoided in women treated with moxifloxacin. Adequate contraceptive measures should be taken.

Breast-feeding

The use of moxifloxacin during breast-feeding is contraindicated. As with other quinolones, moxifloxacin has been shown to cause lesions in the cartilage of the weight bearing joints of immature animals. Preclinical data indicate that small amounts of moxifloxacin passes into breast milk.

Fertility

No specific studies with moxifloxacin in humans have been conducted to evaluate effects on fertility. Animal studies do not indicate impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed. However, fluoroquinolones including moxifloxacin may cause impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness; acute, transient loss of vision, see section 4.8) or acute and short lasting loss of consciousness (syncope, see section 4.8). Patients should be advised to see how they react to moxifloxacin before driving or operating machinery.

4.8 Undesirable effects

Adverse reactions based on all clinical trials with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below. Of note, the majority of available safety data on moxifloxacin has been generated in patients with conditions other than tuberculosis in studies of less than three weeks duration.

Adverse events considered at least possibly related to moxifloxacin treatment are listed below by body system, organ class and frequency. Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis				

Blood and the lymphatic system disorders		Anaemia Leucopenia Neutropenia Thrombocytopenia Thrombocythaemia Blood eosinophilia Prothrombin time prolonged/INR increased		Prothrombin level increased/INR decreased Agranulocytosis Pancytopenia	
Immune system disorders		Allergic reaction (see section 4.4)	Anaphylaxis incl. very rarely life-threatening shock (see section 4.4) Allergic oedema / angioedema (including laryngeal oedema, potentially life-threatening, see section 4.4)		
Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolic and nutrition disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	Hypoglycaemia Hypoglycaemic coma	
Psychiatric disorders*		Anxiety reactions Psychomotor hyperactivity/ agitation	Emotional lability Depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts, or suicide attempts, see section 4.4) Hallucination Delirium	Depersonalisation Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts, or suicide attempts, see section 4.4)	
Nervous system disorders*	Headache Dizziness	Paraesthesia-and dysaesthesia Taste disorders (incl.ageusia in very rare cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo) Seizures incl. grand mal convulsions (see section 4.4) Disturbed attention	Hyperaesthesia	

			Speech disorders Amnesia Peripheral neuropathy and polyneuropathy		
Eye disorders*		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions, see section 4.4)	Photophobia	Transient loss of vision (especially in the course of CNS reactions, see sections 4.4 and 4.7) Uveitis and bilateral acute iris transillumination (see section 4.4)	
Ear and labyrinth disorders*			Tinnitus Hearing impairment incl. deafness (usually reversible)		
Cardiac disorders**	QT prolongation in patients with hypokalaemia (see sections 4.3 and 4.4)	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris	Ventricular tachyarrhythmias Syncope (i.e., acute and short lasting loss of consciousness)	Unspecified arrhythmias Torsade de pointes (see section 4.4) Cardiac arrest (see section 4.4)	
Vascular disorders		Vasodilatation	Hypertension Hypotension	Vasculitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea (including asthmatic conditions)			
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (incl. pseudo-membranous colitis, in very rare cases associated with life-threatening complications, see section 4.4)		
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	Fulminant hepatitis, potentially leading to life-threatening liver failure (incl. fatal cases, see section 4.4)	
Skin and subcutaneous		Pruritus Rash		Bullous skin reactions like	Acute generalised exanthematous

tissue disorders		Urticaria Dry skin		Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening, see section 4.4)	pustulosis (AGEP)
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendinitis (see section 4.4) Muscle cramp Muscle twitching Muscle weakness	Tendon rupture (see section 4.4) Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis (see section 4.4)	Rhabdomyolysis
Renal and urinary disorders		Dehydration	Renal impairment (including increase in BUN and creatinine) Renal failure (see section 4.4)		
General disorders and administration site conditions*		Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvis and extremities) Sweating	Oedema		

*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 tendinitis, 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).

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with moxifloxacin: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia, rhabdomyolysis, photosensitivity reactions (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

Single oral overdoses up to 2.8 g were not associated with any serious adverse events.

Therapy

No specific countermeasures after accidental overdose are recommended. General symptomatic therapy should be initiated. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Concomitant administration of charcoal with a dose of 400mg oral moxifloxacin will reduce

systemic availability of the drug by more than 80%. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure. About 3% and 9% of the dose of moxifloxacin, as well as about 2% and 4.5% of its glucuronide metabolite are removed by continuous ambulatory peritoneal dialysis and haemodialysis, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01 MA14

Mechanism of action

Moxifloxacin 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 moxifloxacin against *M. tuberculosis* results from the inhibition of the DNA gyrase, encoded by the *gyrA* and *gyrB* genes.

The wild-type moxifloxacin MIC distribution for clinical isolates of *M. tuberculosis* has been reported by different investigators to range between 0.03-1 mg/L. 0.5 mg/L has been suggested as a susceptibility breakpoint. 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 experience

An individual patient data meta-analysis of 50 observational and experimental studies from 25 countries showed that of 12 030 patients, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died. Compared with failure or relapse, treatment success was positively associated with the use of linezolid (adjusted risk difference 0·15, 95% CI 0·11 to 0·18), levofloxacin (0·15, 0·13 to 0·18), carbapenems (0·14, 0·06 to 0·21), moxifloxacin (0·11, 0·08 to 0·14), bedaquiline (0·10, 0·05 to 0·14), and clofazimine (0·06, 0·01 to 0·10). There was a significant association between reduced mortality and use of linezolid (-0·20, -0·23 to -0·16), levofloxacin (-0·06, -0·09 to -0·04), moxifloxacin (-0·07, -0·10 to -0·04), or bedaquiline (-0·14, -0·19 to -0·10). It was concluded that, although inferences are limited by the observational nature of the data, treatment outcomes of multidrug-resistant tuberculosis were significantly better with use of later generation fluoroquinolones, such as moxifloxacin, as well as with use of linezolid, bedaquiline, clofazimine, and carbapenems.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB315 trade name] have been determined after administration of a single tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value (± standard deviation)**
Maximum concentration (C_{max})	1.92 µg/ml (± 0.40)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	29.6 µg.h/ml (± 4.7)
Time to attain maximum concentration (t_{max})	2.11 (± 1.12) h

Pharmakokinetics of Moxifloxacin

Moxifloxacin	
Absorption	
Absolute bioavailability	91%

Oral bioavailability	Rapid and almost complete absorption after oral administration
Food effect	Absorption not affected by concomitant food intake (high fat meal)
Distribution	
General	Rapid distribution to extravascular spaces Steady-state within 3 days (with 400mg once daily regimen)
Volume of distribution at steady state (mean)	Approximately 2 L/kg
Plasma protein binding	Approximately 40-42 %, independent of the concentration of the drug. Mainly bound to serum albumin

Tissue	**Concentration**	**Site: Plasma ratio**
Plasma	3.1 mg/L	-
Saliva	3.6 mg/L	0.75 – 1.3
Blister fluid	1.6[1] mg/L	1.7[1]
Bronchial mucosa	5.4 mg/kg	1.7 – 2.1
Alveolar macrophages	56.7 mg/kg	18.6 – 70.0
Epithelial lining fluid	20.7 mg/L	5 - 7
Maxillary sinus	7.5 mg/kg	2.0
Ethmoid sinus	8.2 mg/kg	2.1
Nasal polyps	9.1 mg/kg	2.6
Interstitial fluid	1.0[2] mg/L	0.8 – 1.4[2,3]
Female genital tract*	10.2[4] mg/kg	1.72[4]

*intravenous administration of a single 400mg dose
[1] 10 h after administration
[2] unbound concentration
[3] from 3 h up to 36 h post dose
[4] at the end of infusion

Metabolism	
	Phase II biotransformation: 52% of an oral dose as glucuronide and sulfate conjugation
Active metabolites	None
Elimination	
Elimination half life	Approximately 12 hours
Mean systemic clearance (Cl/F)	179 to 246 mL/min (following a 400 mg dose) Renal clearance about 24 – 53 mL/min suggesting partial tubular reabsorption of the drug from the kidneys
% of dose excreted in urine	Approximately 19 % for unchanged drug Approximately 2.5 % for the sulfate-metabolite Approximately 14 % for the glucuronide-metabolite
% of dose excreted in faeces	Approximately 25 % of unchanged drug Approximately 36% for the sulphate-metabolite No recovery for the glucuronide-metabolite
Pharmacokinetic linearity	Linear in the range of 50 - 1200 mg after single dose and up to 600 mg after once daily dosing over 10 days.
Drug interactions	
Metabolizing enzymes	No interactions with drugs undergoing Phase I biotransformation involving

	cytochrome P450 enzymes No indication of oxidative metabolism

Elderly and patients with low body weight

Higher plasma concentrations are observed in healthy volunteers with low body weight (such as women) and in elderly volunteers.

Renal impairment

The pharmacokinetic properties of moxifloxacin are not significantly different in patients with renal impairment (including creatinine clearance> 20 mL/min/1.73 m^2). As renal function decreases, concentrations of the M2 metabolite (glucuronide) increase by up to a factor of 2.5 (with a creatinine clearance of < 30 mL/min/1.73 m^2).

Hepatic impairment

On the basis of the pharmacokinetic studies carried out so far in patients with liver failure (Child Pugh A, B, C), it is not possible to determine whether there are any differences compared with healthy volunteers. Impaired liver function was associated with higher exposure to M1 in plasma, whereas exposure to parent drug was comparable to exposure in healthy volunteers.

5.3 Preclinical safety data

Effects on the haematopoetic system (slight decreases in the number of erythrocytes and platelets) were seen in rats and monkeys. As with other quinolones, hepatotoxicity (elevated liver enzymes and vacuolar degeneration) was seen in rats, monkeys and dogs. In monkeys, CNS toxicity (convulsions) occurred. These effects were seen only after treatment with high doses of moxifloxacin or after prolonged treatment.

Moxifloxacin, like other quinolones, was genotoxic in *in vitro* tests using bacteria or mammalian cells. Since these effects can be explained by an interaction with the gyrase in bacteria and - at higher concentrations - by an interaction with the topoisomerase II in mammalian cells, a threshold concentration for genotoxicity can be assumed. In *in vivo* tests, no evidence of genotoxicity was found despite the fact that very high moxifloxacin doses were used. Thus, a sufficient margin of safety to the therapeutic dose in man can be provided. Moxifloxacin was non-carcinogenic in an initiation-promotion study in rats.

Moxifloxacin was proven to be devoid of phototoxic and photogenotoxic properties when tested in a comprehensive programme of *in vitro* and *in vivo* studies. Under the same conditions other quinolones induced effects.

At high concentrations, moxifloxacin is an inhibitor of the rapid component of the delayed rectifier potassium current of the heart and may thus cause prolongations of the QT interval. Toxicological studies performed in dogs using oral doses of 90 mg/kg leading to plasma concentrations 16 mg/L caused QT prolongations, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50-fold the human dose (> 300 mg/kg), leading to plasma concentrations of ≥ 200 mg/L (more than 40-fold the therapeutic level), reversible, non-fatal ventricular arrhythmias were seen.

Quinolones are known to cause lesions in the cartilage of the major diarthrodial joints in immature animals. The lowest oral dose of moxifloxacin causing joint toxicity in juvenile dogs was four times the maximum recommended therapeutic dose of 400 mg (assuming a 50 kg bodyweight) on an mg/kg basis, with plasma concentrations two to three times higher than those at the maximum therapeutic dose.

Toxicity tests in rats and monkeys (repeated dosing up to six months) revealed no indication regarding an oculotoxic risk. In dogs, high oral doses (≥ 60 mg/kg) leading to plasma concentrations ≥ 20 mg/L caused changes in the electroretinogram and in isolated cases an atrophy of the retina.

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Studies in rats (p.o. and i.v.) and monkeys (p.o.) did not show evidence of teratogenicity or impairment of fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in foetuses of rabbits but only at a dose (20 mg/kg i.v.) which was associated with severe maternal toxicity. There was an increase in the incidence of abortions in monkeys and rabbits at human therapeutic plasma concentrations. In rats, decreased foetal weights, an increased prenatal loss, a slightly increased duration of pregnancy and an increased spontaneous

activity of some male and female offspring was observed at doses which were 63 times the maximum recommended dose on an mg/kg basis with plasma concentrations in the range of the human therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Croscarmellose sodium,
colloidal anhydrous silica,
magnesium stearate,
microcrystalline cellulose,
povidone

Film coat : Hypromellose,
iron oxide red,
iron oxide yellow,
macrogol (PEG),
titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

The primary packs are blister cards of 10 tablets (comprised of plain aluminium foil- aluminium foil). One blister card per carton.

6.6 Special precautions for disposal and other handling

Preparation and administration - extemporaneous formulation for children

Two small bowls, drinking water, a teaspoon and a 10-mL oral syringe with 1-mL markings are needed for preparing the extemporaneous formulation. The following steps should be applied:

1. One 400-mg tablet should be disintegrated in a small bowl in 10 mL of drinking water by stirring gently.
2. The required portion of the mixture (see dosing table in 4.2, above) should be withdrawn with the syringe.
3. The withdrawn mixture should be mixed with additional liquid or semi-solid food to mask the bitter taste.
4. The mixture should be administered immediately to the child.
5. Any unused mixture must be discarded.

7. SUPPLIER

Hetero Labs Limited, Unit 5
Survey No 439,440,441 & 458.TSIIC Formulation SEZ,
Polepally Village,
Jadcherla (M),
Mahaboob Nagar District
Telangana – 509 301,

India.

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB315

9. DATE OF PREQUALIFICATION

20 July 2017

10. DATE OF REVISION OF THE TEXT

July 2021

References

General reference sources for this SmPC include:

Avelox ® SmPC. Available at: https://www.medicines.org.uk/emc/medicine/11841

Avelox® U.S. Prescribing Information, Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021085s064,021277s060lbl.pdf

Guidelines for the programmatic management of drug-resistant tuberculosis, 2014 update. Available at: https://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf?sequence=1

Quinolones and Fluoroquinolones Art 31 referral; Amendments to relevant sections of the summary of product characteristics and package leaflets, 2018. Available at https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-annex-iii_en.pdf

Section 4.2:

Guidelines for multidrug-and rifampicin-resistant tuberculosis, 2018 update. Available at https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf?ua=1

Section 4.5

Weiner M et al. Antimicrob Agents Chemother 2007, 51:2861-2866

Nijland HM et al. Clin Infect Dis 2007; 45:1001-1007

Dooley K et al. Antimicrob Agents Chemother 2008; 52: 4037-4042

Section 4.8

Ball P et al. Clin Ther 2004; 26: 940 - 950

Section 5.1

Gillespie SH and Billington O. J Antimicrob Chemother 1999; 44:393-395

Hu Y et al. Antimicrob Agents Chemother 2003; 47:653-657

Ängeby K et al. J Antimicrob Chemother 2010; 65: 946–952

Rodriguez JC et al. Int J Antimicrob Agents 2001; 3:229-31

Rodriguez JC et al. Int J Antimicrob Agents 2002; 20:464-67

Van Ingen J et al. J Clin Microbiol 2010; 48:2749-2753

Gumbo T Antimicrob Agents Chemother 2010; 54:1484-1491

Von Groll A et al. Antimicrob Agents Chemother 2009; 53:4498-4500

Dorman SE et al. Am J Respir Crit Care Med 2009; 180: 273-280

Conde MB et al. Lancet 2009; 373: 1183–1189

Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017. Lancet 2018;392:821-834.

All weblinks accessed 11 March 2019

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines