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

[TB341 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

Excipients with potential clinical effect

Each tablet contains 5.0 mg anhydrous lactose and 230.17 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

Pale red, capsule-shaped, film-coated tablets. They are biconvex (rounded on top and bottom) with a beveled edge. The tablets have 'M400' debossed (stamped into) one side and a break line on the other side.

The break line can be used to divide [TB341 trade name] into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB341 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis* including in regimens for drug-resistant tuberculosis.

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

4.2 Posology and method of administration

Treatment with [TB341 trade name] should be initiated and monitored by a health care provider experienced in the management of multidrug-resistant *Mycobacterium tuberculosis* infection.

[TB341 trade name] should always be used in combination with other tuberculosis medicines. Consideration should be given to WHO guidelines when selecting the appropriate combination regimen.

Patients should be advised to take [TB341 trade name] exactly as prescribed and to complete the full course.

Posology

Standard-dose treatment

Patients weighing at least 24 kg

The recommended dose is one 400-mg tablet once daily.

Children and adolescents weighing less than 24 kg

The recommended daily dose in children is 10–15 mg/kg bodyweight. [TB341 trade name] is not suitable for children weighing less than 24 kg and they should be given other formulations, e.g. dispersible tablets containing 100 mg moxifloxacin.

If a suitable formulation is not available, an extemporaneous preparation may be made using moxifloxacin 400-mg 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.

High-dose treatment

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

Patients weighing at least 30 kg

Dosing recommendations for high-dose moxifloxacin treatment

Body weight	**Number of 400-mg tablets**	**Dose in mg**
30 to less than 36 kg	1 *or* 1½ tablets daily	400 *or* 600 mg daily
36 to less than 46 kg	1½ tablets daily	600 mg daily
46 to less than 56 kg	1½ *or* 2 tablets daily	600 *or* 800 mg daily
56 kg and over	2 tablets daily	800 mg daily

Therapeutic drug monitoring is advised for doses at the upper and lower ends of the range to minimise adverse therapeutic consequences of over-exposure or under-exposure.

Children and adolescents weighing less than 30 kg

High-dose moxifloxacin treatment is not recommended for patients weighing less than 30 kg.

Treatment duration

The duration of tuberculosis treatment depends on the regimen chosen, the patient's clinical and radiographical responses, smear and culture results, and susceptibility of *Mycobacterium tuberculosis* isolates from the patient or the suspected source case.

Special populations

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.

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 [TB341 trade name] and reduce its effectiveness.

The patient should take a missed dose if it was due fewer than 12 hours since the dose was due. 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 [TB341 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

[TB341 trade name] should be swallowed whole with sufficient liquid, and it may be taken with food or between meals.

See section 6.6 for extemporaneous preparation if a suitable preparation for children is not available.

4.3 Contraindications

[TB341 trade name] is contraindicated in patient with:

- hypersensitivity to moxifloxacin, other quinolones or fluoroquinolone antibacterials or to any excipients listed in section 6.1
- a history of tendon disease or a serious adverse reaction related to quinolone or fluoroquinolone treatment
- transaminases increased to more than 5 times the upper limit of normal

QT prolongation has occurred following moxifloxacin treatment. Moxifloxacin is therefore contraindicated in patients with:

- 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

Prolongation of QTc interval

Moxifloxacin has prolonged the QTc interval on the electrocardiogram in some patients. In ECGs obtained in the clinical trial programme, QTc prolongation with moxifloxacin was 6 ms ± 26 ms, 1.4% compared to baseline. As women may have a longer baseline QTc interval, they may be more sensitive to QTc-prolonging medicines. 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. ECGs and serum potassium levels should be closely monitored.

Medicines that can reduce potassium levels should be used with caution in patients receiving moxifloxacin (see also section 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 increase the 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.

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 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 and allergic reactions

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

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 before 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 if there is any indication of liver dysfunction.

Patients with 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.

Severe cutaneous reactions

Severe cutaneous adverse reactions including toxic epidermal necrolysis (Lyell's syndrome), Stevens Johnson syndrome and acute generalised exanthematous pustulosis, which could be life-threatening or fatal, have been reported with moxifloxacin (see section 4.8). Patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms of these reactions appear, moxifloxacin should be discontinued immediately, and alternative treatment considered. If the patient has developed a serious cutaenous reaction with the use of moxifloxacin, the patient should never receive moxifloxacin again.

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 paraesthesia, hypoaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones including moxifloxacin. Patients receiving moxifloxacin should be advised to inform their health care provider 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 dose of moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-endangering behaviour such as suicide attempts. If 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 colitis

Diarrhoea, particularly if severe, persistent or bloody, during or after treatment with moxifloxacin, may be a symptom of antibiotic-associated colitis, which can be life-threatening. Therefore, if antibiotic-associated colitis is suspected or confirmed, moxifloxacin must be stopped immediately, and diarrhoea should be appropriately managed without delay. Products inhibiting peristalsis are contraindicated in this situation.

Myasthenia gravis

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

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with a quinolone or a fluoroquinolone 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 or limbs should be 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 or mitral valve regurgitation or incompetence after fluoroquinolone treatment, particularly in older people. Therefore, moxifloxacin should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with a family history of aneurysm disease or congenital heart disease, or in patients with aortic aneurysm or dissection or heart valve disease, or in the presence of other risk factors or conditions predisposing to these conditions (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet'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.

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 the patient has any effects on the eyes, an eye specialist should be consulted immediately.

Dysglycaemia

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia have been reported with moxifloxacin. In moxifloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients treated concomitantly with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of severe hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Photosensitivity

Quinolones can 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 or strong sunlight during treatment with moxifloxacin.

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.

Excipients

[TB341 trade name] contains a small lactose. Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

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.

QT-interval prolonging agents

An additive effect on QT interval prolongation of moxifloxacin and other medicines that prolong the QT interval may occur. This effect might increase the risk of ventricular arrhythmias, notably torsade de pointes. Therefore, moxifloxacin should be used with caution in patients treated with any of the following (see also section 4.4):

- antiarrhythmics (e.g. *amiodarone, disopyramide, dofetilide, hydroquinidine, ibutilide, quinidine, sotalol* ,),
- antipyschotics (e.g. *phenothiazine antipsychotics, haloperidol, pimozide, sertindole, 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 drugs (e.g. *bepridil, cisapride, diphemanil*, intravenous *vincamine*).

Potassium lowering agents

Moxifloxacin should be used with caution in patients who are taking medicines that can reduce potassium levels (e.g. loop and thiazide-type diuretics, laxatives and high doses of enemas, corticosteroids, amphotericin B).

Medicines causing bradycardia

Moxifloxacin should be used with caution in patients who are taking medicines associated with clinically significant bradycardia.

Corticosteroids

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

Medicines containing aluminium, iron or magnesium

Formation of chelates with aluminium, iron and magnesium may inhibit the absorption of moxifloxacin. Taking medicines containing these cations and moxifloxacin at around the same time may decrease moxifloxacin exposure by 25–60%. An interval of at least 6 hours should be left between administration of moxifloxacin and administration of antacids containing *magnesium* or *aluminium, didanosine* tablets, *sucralfate* and medicines containing *iron* or *zinc*.

Charcoal

Concomitant administration of *charcoal* with 400 mg moxifloxacin led to pronounced reduction of moxifloxacin absorption and reduced its systemic availability by more than 80%. Therefore, the concomitant use of the two is not recommended (except for overdose, see also section 4.9).

Glibenclamide

In studies in diabetic volunteers, concomitant administration of 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 increased oral *anticoagulant* activity have been reported in patients receiving antibiotics, especially fluoroquinolones, macrolides, tetracyclines, sulfamethoxazole/trimethoprim 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 similar anticoagulants.

4.6 Fertility, pregnancy and breastfeeding

Women of child-bearing potential

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

Pregnancy

[TB341 trade name] can be used during pregnancy after fully considering the woman's individual circumstances. Although information is limited, successful pregnancy outcomes have been recorded after the use of moxifloxacin as part of a combination regimen for treating drug-resistant tuberculosis.

Reversible joint injuries have been reported in children receiving some quinolones; however, this effect has not been reported among exposed fetuses. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Tuberculosis can be particularly dangerous in pregnancy and it should be managed with effective treatment. The decision on treatment during pregnancy should take into account the grave danger of tuberculosis to the patient and the fetus as well as the possibility of harm to the fetus. Close monitoring during and after pregnancy is important to ensure that any concerns are dealt with promptly.

Breast-feeding

As with other quinolones, moxifloxacin can cause lesions in the cartilage of the weight-bearing joints of immature animals. Preclinical data indicate that small amounts of moxifloxacin pass into breast milk.

The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for moxifloxacin and any potential adverse effects on the breast-fed child from moxifloxacin or from the mother’s tuberculosis.

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%.

The undesirable effects of moxifloxacin are listed below by body system or organ. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and infestations

Common	superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis

Blood and lymphatic disorders

Uncommon	anaemia; eosinophilia; leucopenia; neutropenia; prolonged prothrombin time/INR increased; thrombocythaemia; thrombocytopenia
Not known	agranulocytosis; pancytopenia; increased prothrombin level/INR decreased

Immune system disorders

Uncommon	allergic reaction†
Not known	allergic oedema/angioedema† (including potentially life-threatening laryngeal oedema); anaphylaxis including very rarely life-threatening shock†

Endocrine disorders

Very rare	syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolic and nutrition disorders

Uncommon	hyperlipidaemia
Rare	hyperglycaemia; hyperuricaemia
Very rare	hypoglycaemia; hypoglycaemic coma†

Psychiatric disorders*

Uncommon	anxiety reactions; psychomotor hyperactivity/agitation
Rare	delirium; depression (in very rare cases potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts, or suicide attempts†); emotional lability; hallucination
Very rare	depersonalisation; psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/thoughts, or suicide attempts†)

Nervous system disorders*

Common	headache; dizziness
Uncommon	confusion and disorientation; paraesthesia and dysaesthesia; sleep disorders (predominantly insomnia); somnolence; taste disorders (including ageusia in very rare cases); tremor; vertigo
Rare	abnormal dreams; amnesia; disturbed attention; disturbed coordination (including gait disturbances, especially due to dizziness or vertigo); hypoaesthesia; peripheral neuropathy and polyneuropathy; seizures including grand mal convulsions†; smell disorders (including anosmia); speech disorders
Very rare	hyperaesthesia

Eye disorders*

Uncommon	visual disturbances including diplopia and blurred vision (especially in the course of CNS reactions[†])
Rare	photophobia
Very rare	transient loss of vision (especially in the course of CNS reactions[#]); uveitis and bilateral acute iris transillumination[†]

Ear and labyrinth disorders*

Rare	hearing impairment including deafness (usually reversible); tinnitus

Cardiac disorders**

Common	QT-interval prolongation in patients with hypokalaemia[§]
Uncommon	angina pectoris, atrial fibrillation; palpitations; QT-interval prolongation[†]; tachycardia
Rare	syncope (i.e. acute and short-lasting loss of consciousness); ventricular tachyarrhythmias
Very rare	cardiac arrest[†]; torsade de pointes[†]; unspecified arrhythmias

Vascular disorders

Uncommon	vasodilatation
Rare	hypertension; hypotension
Very rare	vasculitis

Respiratory, thoracic and mediastinal disorders

Uncommon	dyspnoea (including asthmatic conditions)

Gastrointestinal disorders

Common	diarrhoea; gastrointestinal and abdominal pains; nausea; vomiting
Uncommon	constipation; decreased appetite and food intake; dyspepsia; flatulence; gastritis; increased amylase
Rare	antibiotic associated colitis (including pseudomembranous colitis, in very rare cases associated with life-threatening complications[†]); dysphagia; stomatitis

Hepatobiliary disorders

Common	increase in transaminases
Uncommon	hepatic impairment (including LDH increase); increased bilirubin; increased gamma-glutamyl-transferase; increased blood alkaline phosphatase
Rare	hepatitis (predominantly cholestatic); jaundice
Very rare	fulminant hepatitis, potentially leading to life-threatening liver failure (including fatal cases[†])

Skin and subcutaneous tissue disorders

Uncommon	dry skin; pruritus; rash; urticaria
Very rare	bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening[†])
Not known	acute generalised exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders*

Uncommon	arthralgia; myalgia
Rare	muscle cramp; muscle twitching; muscle weakness; tendinitis (†)
Very rare	arthritis; exacerbation of symptoms of myasthenia gravis[†]; muscle rigidity; tendon rupture[†]
Not known	rhabdomyolysis

Renal and urinary disorders

Uncommon	dehydration
Rare	renal failure†; renal impairment (including increase in BUN and creatinine)

General disorders and administration site conditions*

Uncommon	feeling unwell (predominantly asthenia or fatigue); painful conditions (including pain in back, chest, pelvis and extremities); sweating
Rare	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 impaired 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).
† See section 4.4
§ See sections 4.3 and 4.4
# See sections 4.4 and 4.7

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

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

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

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.

The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic moxifloxacin exposure. Concomitant administration of charcoal with a dose of 400 mg moxifloxacin can reduce systemic availability of the drug by more than 80%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA14

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 and 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.

TB-PRACTECAL was an open-label, phase 2–3, multi-centre, randomised, controlled, non-inferiority trial to evaluate the efficacy and safety of three 24-week, oral regimens for the treatment of rifampicin-resistant tuberculosis. Patients 15 years and older who had rifampicin-resistant pulmonary tuberculosis were enrolled. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9- to 20-month standard-care (SoC) regimen. Moxifloxacin was administered at a dose of 400 mg once daily for 24 weeks.

The TB-PRACTECAL trial stopped enrolling patients soon after its independent data safety and monitoring board indicated that the BPaLM regimen is superior to the SoC. Of 128 patients in the modified intention-to-treat analysis, 11% of the patients in the BPaLM group and 48% of those in the SoC group had a primary-outcome event, either death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis at 72 weeks after randomisation. The risk difference (96.6% confidence interval [CI]) was -37% (-53 to -22).

5.2 Pharmacokinetic properties

The absorption characteristics of [TB341 trade name] have been determined in healthy subjects after [TB341 trade name] in healthy volunteers in the fasting state as follows:

Characteristic	**Arithmetic mean ± standard deviation**
Maximum concentration (C_{max})	3.089 ± 0.828 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	33.794 ± 5.272 µg·h/mL
Time to attain maximum concentration (T_{max}) #	1.15 ± 0.92 hours

#median (range)

Pharmacokinetics 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	

<table>
<tr><td>General</td><td>Rapid distribution to extravascular spaces
Steady-state within 3 days (with 400 mg once daily regimen)</td></tr>
<tr><td>Volume of distribution at steady state (mean)</td><td>Approximately 2 L/kg</td></tr>
<tr><td>Plasma protein binding</td><td>Approximately 40–42%, independent of the concentration of the drug.
Mainly bound to serum albumin
<table>
<tr><th>Tissue</th><th>Concentration</th><th>Site/Plasma ratio</th></tr>
<tr><td>Plasma</td><td>3.1 mg/L</td><td>–</td></tr>
<tr><td>Saliva</td><td>3.6 mg/L</td><td>0.75–1.3</td></tr>
<tr><td>Blister fluid</td><td>1.6 mg/L[1]</td><td>1.7[1]</td></tr>
<tr><td>Bronchial mucosa</td><td>5.4 mg/kg</td><td>1.7–2.1</td></tr>
<tr><td>Alveolar macrophages</td><td>56.7 mg/kg</td><td>18.6–70.0</td></tr>
<tr><td>Epithelial lining fluid</td><td>20.7 mg/L</td><td>5–7</td></tr>
<tr><td>Maxillary sinus</td><td>7.5 mg/kg</td><td>2.0</td></tr>
<tr><td>Ethmoid sinus</td><td>8.2 mg/kg</td><td>2.1</td></tr>
<tr><td>Nasal polyps</td><td>9.1 mg/kg</td><td>2.6</td></tr>
<tr><td>Interstitial fluid</td><td>1.0 mg/L[2]</td><td>0.8–1.4[2,3]</td></tr>
<tr><td>Female genital tract*</td><td>10.2 mg/kg[4]</td><td>1.72[4]</td></tr>
<tr><td colspan="3">*intravenous administration of a single 400-mg dose
[1] 10 hours after administration
[2] unbound concentration
[3] from 3 hours up to 36 hours after dosing
[4] at the end of infusion</td></tr>
</table></td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td></td><td>Phase II biotransformation: 52% of an oral dose as glucuronide and sulfate conjugation</td></tr>
<tr><td>Active metabolites</td><td>None</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Elimination half life</td><td>Approximately 12 hours</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>179 to 246 mL/minute (following 400-mg dose)
Renal clearance about 24–53 mL/minute, suggesting partial tubular reabsorption of the drug from the kidneys</td></tr>
<tr><td>% of dose excreted in urine</td><td>Approximately 19% for unchanged drug
Approximately 2.5% for the sulfate-metabolite
Approximately 14% for the glucuronide-metabolite</td></tr>
<tr><td>% of dose excreted in faeces</td><td>Approximately 25% of unchanged drug
Approximately 36% for the sulphate-metabolite
No recovery for the glucuronide-metabolite</td></tr>
<tr><td>Pharmacokinetic linearity</td><td>Linear in the range of 50–1200 mg after single dose and up to 600 mg after once-daily dosing over 10 days.</td></tr>
<tr><td colspan="2">Drug interactions</td></tr>
<tr><td>Metabolising enzymes</td><td>No interactions with drugs undergoing Phase I biotransformation involving cytochrome P450 enzymes
No indication of oxidative metabolism</td></tr>
</table>

Special populations

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 more than 20 mL/minute/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 less than 30 mL/minute/1.73 m^2).

Hepatic impairment

On the basis of the pharmacokinetic studies 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 of moxifloxacin 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 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 animal tests, no evidence of genotoxicity was found despite the use of very high moxifloxacin doses. 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 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 inhibits the rapid component of the delayed rectifier potassium current of the heart and may thus prolong the QT interval. Toxicological studies in dogs using oral doses of 90 mg/kg, leading to plasma concentrations 16 mg/L, caused QT prolongation, but no arrhythmias. Only after very high cumulative intravenous administration of more than 50-fold the human dose (more than 300 mg/kg), leading to plasma concentrations of at least 200 mg/L (more than 40-fold the therapeutic level), reversible, non-fatal ventricular arrhythmias were seen.

Quinolones can 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 4 times the maximum recommended therapeutic dose of 400 mg (assuming a 50 kg body weight) on an mg/kg basis, with plasma concentrations 2–3 times higher than those at the maximum therapeutic dose.

Toxicity tests in rats and monkeys (repeated dosing up to 6 months) revealed no oculotoxic risk. In dogs, high oral doses (at least 60 mg/kg), leading to plasma concentrations of at least 20 mg/L, caused changes in the electroretinogram and, in isolated cases, atrophy of the retina.

Reproductive studies in rats, rabbits and monkeys indicate placental transfer of moxifloxacin. Studies in rats (oral and intravenous dosing) and monkeys (oral dosing) did not show teratogenicity or impaired fertility following administration of moxifloxacin. A slightly increased incidence of vertebral and rib malformations was observed in fetuses of rabbits but only at a dose (20 mg/kg intravenously) 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 fetal 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: lactose monohydrate
povidone
anhydrous lactose
croscarmellose sodium
colloidal silicon dioxide
magnesium stearate

Film coat: (Opadry Brown 03B86891)
hypromellose
titanium dioxide
polyethylene glycol
iron oxide red

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30ºC. Protect from light and moisture.

6.5 Nature and contents of container

Blister pack

[TB341 trade name] is available in clear colourless (PVC/PVDC) on aluminium foil blister cards, each containing 5, 7 or 10 tablets.

Available in the following pack sizes: 3 x 5 tablets, 5 x 7 tablets, 3 x 10 tablets and 10 x 10 tablets

Bottle pack

[TB341 trade name] is also available in HDPE container packs of 30 tablets and 500 tablets.

The 30-tablet pack is opaque white 40 cc plastic (HDPE) bottle. The bottle has a white opaque 33 mm childproof plastic (polypropylene) screw cap.

The 500's count container pack is opaque white plastic 950 cc (HDPE) bottle. The bottle has a white opaque 55 mm ribbed plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

Preparation and administration - extemporaneous formulation for children

Extemporaneous preparation for children weighing less than 24 kg

If a suitable formulation is not available, an extemporaneous preparation may be made mixing one moxifloxacin 400-mg tablet in 10 mL water. However, bioavailability of moxifloxacin from an extemporaneous preparation is uncertain.

Two small bowls, drinking water, and a 10-mL oral syringe with 1-mL markings are needed for preparing the extemporaneous formulation. The preparations should be made as follows:

1. One 400-mg tablet should be placed in a small bowl and 10 mL of drinking water, measured using the oral syringe, should be added.
2. The tablet should be disintegrated, and the mixture stirred until the tablet has broken down completely.
3. Using the oral syringe, the required volume of the mixture (see table below) should be withdrawn. The unused mixture in the bowl must be discarded.
4. The mixture in the oral syringe should be added to the second bowl and mixed with a small amount of additional liquid or semi-solid food to mask the bitter taste.
5. The mixture from the second bowl should be given immediately to the child.

Dose of extemporaneous preparation for children weighing up to 24 kg

Child's weight	**Dose as volume of mixture (1 tablet in 10 mL water)**	**Dose in mg**
3 to less than 5 kg	1 mL	40 mg daily
5 to less than 7 kg	2 mL	80 mg daily
7 to less than 10 kg	3 mL	120 mg daily
10 to less than16 kg	5 mL*	200 mg daily
16 to less than 24 kg	5 mL* to 7.5 mL	200–300 mg daily
24 kg and over	(Use tablet)	400 mg (one tablet) daily
* A dose of 200 mg may alternatively be given as half a tablet of [TB341 trade name] by breaking it along the score line.		

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB341

9. DATE OF PREQUALIFICATION

19 June 2018

10. DATE OF REVISION OF THE TEXT

January 2025

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General reference sources for this SmPC include:

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Section 4.5

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Section 5.1

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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