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

[TB395 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120.89 mg bedaquiline fumarate equivalent to 100 mg bedaquiline.

Excipients with potential clinical effect

Each tablet contains about 143 mg of lactose monohydrate.

3. PHARMACEUTICAL FORM

White to off-white, round, uncoated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'MB 1' debossed (stamped into) one side and are plain on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB395 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis*.

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

4.2 Posology and method of administration

Treatment with [TB395 trade name] should be initiated and monitored by a health care provider experienced in the management of multidrug-resistant *Mycobacterium tuberculosis* infection.

Patients should be advised to take [TB395 trade name] exactly as prescribed and to complete the full course.

Posology

A 6-month treatment regimen is recommended for patients with multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis. If a 6-month regimen cannot be used, a 9-month (or longer) regimen may be selected.

For both regimens, bedaquiline is given for the first 6 months, unless the infection does not respond well enough or the patient develops side effects that interrupt the regimen; in such cases bedaquiline treatment may need to be extended.

Recommended doses of bedaquiline for both regimens are shown below.

Dosage for 6-month regimens

6-month regimens comprise bedaquiline with pretomanid and linezolid (with or without moxifloxacin); some guidelines refer to them as BPaL or BPaLM regimens. These regimens should not be used in adolescents and children less than 14 years of age.

Adults and adolescents at least 14 years old

First 8 weeks	bedaquiline 200 mg (2 tablets of [TB395 trade name]) **once daily**
Week 9 onwards	bedaquiline 100 mg (1 tablet of [TB395 trade name]) **once daily**

Alternatively, the dosage regimen shown below for the 9-month regimen (under 'Adults and adolescents weighing at least 30 kg') may be used.

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

Treatment may need to be extended to 9 months depending on how the infection responds and the patient's tolerance to the treatment.

Dosage for 9-month regimens

9-month or longer regimens comprise bedaquiline with levofloxacin or moxifloxacin, ethionamide or linezolid, ethambutol, high-dose isoniazid, pyrazinamide and clofazimine. Bedaquiline is given for the first 6 months of the regimen but may be given for up to 9 months if the initial phase of the regimen is extended from 4 months to 6 months.

Adults and adolescents weighing at least 30 kg

First 2 weeks	bedaquiline 400 mg (4 tablets of [TB395 trade name]) **once daily**
Week 3 onwards	bedaquiline 200 mg (2 tablets of [TB395 trade name]) once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)

Alternatively, the dosage regimen shown above for the 6-month regimen (under 'Adults and adolescents at least 14 years old') may be used.

Children and adolescents weighing 16–30 kg

First 2 weeks	bedaquiline 200 mg (2 tablets of [TB395 trade name]) **once daily**
Week 3 onwards	bedaquiline 100 mg (1 tablet of [TB395 trade name]) once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)

Children and adolescents weighing less than 16 kg

For children weighing less than 16 kg, a dispersible formulation of bedaquiline is preferred, when available.

If a suitable formulation is not available, an extemporaneous preparation may be made using 1 bedaquiline 100 mg tablet (1 tablet of [TB395 trade name]) in 10 mL of water (see instructions in section 6.6). A proportion of the mixture should be given according to the child's weight and age as follows:

Child's weight	**Child's age**	**Treatment duration**	**Volume to be given after dispersing 1 tablet in 10 mL water**	**Dose in mg**
3 to less than 7 kg[1]	0 to less than 3 months	First 2 weeks	3 mL **once daily**	30 mg
		Week 3 onwards	1 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	10 mg
	at least 3 months	First 2 weeks	6 mL **once daily**	60 mg
		Week 3 onwards	2 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	20 mg
7 to less than 10 kg	0 to less than 3 months	First 2 weeks	3 mL **once daily**	30 mg
		Week 3 onwards	1 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	10 mg
	3 to less than 6 months	First 2 weeks	6 mL **once daily**	60 mg

		Week 3 onwards	2 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	20 mg
	at least 6 months	First 2 weeks	8 mL **once daily**	80 mg
		Week 3 onwards	4 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	40 mg
10 to less than 16 kg	3 to less than 6 months	First 2 weeks	6 mL **once daily**	60 mg
		Week 3 onwards	2 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	20 mg
	at least 6 months	First 2 weeks	12 mL[2] **once daily**	120 mg[2]
		Week 3 onwards	6 mL once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)	60 mg

[1] For bedaquiline dosing in preterm and low-birth-weight infants weighing less than 3 kg, and ideally for infants weighing 3 to <5 kg, advice from an expert in paediatric drug-resistant TB should be sought.

[2] To make up this dose, 2 tablets of [TB395 trade name] should be dispersed in 20 mL of water.

Missed doses

If the patient misses a dose of [TB395 trade name] when taking it **daily**, the patient should skip the missed dose and take the next one at the usual time to continue the usual dosing schedule.

If the patient misses a dose of [TB395 trade name] when taking it **3 days each week,** and less than 48 hours have passed since the last dose, the patient should take the dose as soon as possible, take the next dose after 48 hours, and then resume the usual dosing schedule.

Dosage after treatment interruption to manage side effects

Interruption during 6-month regimens

If, because of side effects, the regimen comprising [TB395 trade name] is interrupted for up to 2 consecutive weeks or up to a total of 4 non-consecutive weeks, the treatment duration should be extended to make up for the missed doses. If the interruption is longer, the appropriateness of the treatment should be re-evaluated.

Interruption during 9-month regimens

From week 3 onwards, if [TB395 trade name] is interrupted for 2 weeks or longer because of side effects, the patient should again take the initial higher daily dose before recommencing the lower dose on 3 days each week. How long the initial higher daily dose should be taken depends on the duration of treatment interruption:

Duration of treatment interruption	**Number of days on which initial higher daily dose should be taken**
2 weeks to less than 1 month	3 days
1 month to less than 1 year	7 days
at least 1 year	14 days

Elderly

There are limited clinical data on the use of [TB395 trade name] in elderly patients (see section 5.2).

Infants and young children

The safety and efficacy of [TB395 trade name] have not been established in children younger than 14 years for the 6-month regimens.

Hepatic impairment

No dose adjustment is necessary for [TB395 trade name] in patients with mild or moderate hepatic impairment (see section 5.2). [TB395 trade name] should be used with caution in patients with moderate hepatic impairment (see section 5.2). [TB395 trade name] has not been studied in patients with severe hepatic impairment and is not recommended in this population.

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (creatinine clearance less than 30 mL/minute) or end-stage renal disease requiring haemodialysis or peritoneal dialysis, [TB395 trade name] should be used with caution (see section 5.2).

Method of administration

[TB395 trade name] should be taken with food, because food increases the bioavailability (see section 5.2). [TB395 trade name] tablets should be swallowed whole with water. For patients who cannot swallow tablets, or for children weighing less than 16 kg, tablets may be crushed and mixed with drinking water.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There are no clinical data on the use of bedaquiline to treat:

- extra-pulmonary tuberculosis (e.g. central nervous system, bone)
- infections due to mycobacterial species other than *Mycobacterium tuberculosis*
- latent infection with *Mycobacterium tuberculosis*

To prevent the development of resistance, bedaquiline must only be used as part of a combination regimen for treating multidrug-resistant tuberculosis, as recommended by authoritative guidelines, such as from WHO.

Increased mortality

In a 120-week trial in adults where bedaquiline was given for 24 weeks in combination with a background regimen, more deaths occurred in the bedaquiline group than in the placebo group. The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with bedaquiline treatment; see section 5.1 for more information.

QT prolongation

Bedaquiline prolongs the QTc interval. An electrocardiogram should be obtained before starting treatment and at least monthly during treatment with bedaquiline. Serum potassium, calcium, and magnesium levels should be measured before starting treatment and corrected if abnormal. These electrolytes should be monitored if QT interval is prolonged (see sections 4.5 and 4.8).

Giving bedaquiline with other medicines that prolong the QTc interval (including delamanid and levofloxacin) may prolong the QT interval further (see section 4.5). Caution is recommended when prescribing bedaquiline with medicines that can prolong the QT interval.

If clofazimine needs to be given with bedaquiline, clinical monitoring, including frequent electrocardiogram assessment, is recommended (see section 4.5).

[TB395 trade name] treatment is not recommended in patients with the following, unless the benefits of bedaquiline are considered to outweigh the potential risks:

- Heart failure
- QT interval as corrected by the Fridericia method (QTcF) exceeds 450 ms (confirmed by repeat electrocardiogram)
- A personal or family history of congenital QT interval prolongation
- A history of, or ongoing, bradyarrhythmia
- A history of torsade de pointes
- A history of, or ongoing hypothyroidism
- Concomitant administration of fluoroquinolone antibiotics that can prolong QT interval significantly (e.g. gatifloxacin and sparfloxacin)
- Hypokalemia

[TB395 trade name] must be discontinued if the patient develops:

- Clinically significant ventricular arrhythmia
- A QTcF interval exceeding 500 ms (confirmed by repeat electrocardiogram)

If syncope occurs, an electrocardiogram should be obtained to detect any QT interval prolongation.

Hepatotoxicity

In clinical trials where bedaquiline was given with a background regimen, a rise in transaminases or aminotransferase was accompanied by total bilirubin at least 2 times the upper limit of normal (see section 4.8).

Liver function should be monitored throughout treatment since increases in liver enzymes appeared slowly and levels increased gradually over a 24-week course. Symptoms and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) should be monitored at baseline, monthly during treatment, and as needed. If AST or ALT exceeds 5 times the upper limit of normal, then the regimens should be reviewed and [TB395 trade name] and/or any hepatotoxic background medicine should be discontinued.

Other hepatotoxic medicines and alcohol should be avoided while on [TB395 trade name], especially in patients with diminished hepatic reserve.

Paediatric patients

In adolescents weighing between 30 and 40 kg, average exposure is predicted to be higher compared to adults (see section 5.2). This may increase the risk of QT interval prolongation or hepatotoxicity.

Excipients

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.

Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

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

The elimination of bedaquiline has not been fully characterised in vivo. CYP3A4 is the major isoenzyme involved in vitro in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2). Urinary excretion of bedaquiline is negligible. Bedaquiline and M2 are not substrates or inhibitors of P-glycoprotein.

CYP3A4 inducers

Co-administration of bedaquiline and moderate or strong CYP3A4 inducers, e.g. carbamazepine, efavirenz, etravirine, phenytoin, rifamycins (including rifampicin, rifapentine and rifabutin), and St John's wort (*Hypericum perforatum*), should be avoided. This is because CYP3A4 induction may reduce bedaquiline levels and therefore its therapeutic effect.

In an interaction study of single-dose bedaquiline and once-daily rifampicin (strong inducer) in healthy adults, the exposure (area under the concentration–time plot, AUC) of bedaquiline was reduced by around 50%.

CYP3A4 inhibitors

Co-administration of bedaquiline and CYP3A4 inhibitors does not have a clinically relevant effect on bedaquiline exposure. Therefore, the co-administration of bedaquiline and CYP3A4 inhibitors is allowed, and no dose adjustment is needed.

Short-term co-administration of bedaquiline with ketoconazole or clarithromycin (potent CYP3A4 inhibitors) in healthy adults increased bedaquiline's exposure (AUC) by around 20% and 14%, respectively. A more pronounced effect on bedaquiline may occur during prolonged co-administration of ketoconazole or other CYP3A4 inhibitors. See also under 'QT-interval prolonging medicines', below.

There are no safety data from bedaquiline multiple-dose trials which used a dose higher than the indicated dose.

Other tuberculosis medicines

Short-term co-administration of bedaquiline with *isoniazid/pyrazinamide* in healthy adults did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with bedaquiline.

In a placebo-controlled clinical study in patients with multidrug-resistant *Mycobacterium tuberculosis* infection, no major impact was found of co-administration of bedaquiline on the pharmacokinetics of cycloserine, ethambutol, kanamycin, ofloxacin or pyrazinamide.

Antiretroviral medicines

In an interaction study of single-dose bedaquiline and multiple-dose lopinavir/ritonavir in adults, exposure (AUC) to bedaquiline was increased by about 22%. Long-term co-administration of bedaquiline as part of a combination therapy and lopinavir/ritonavir in patients co-infected with HIV resulted in a mild increase in mean bedaquiline exposure at Week 24 compared to a subgroup without HIV co-infection. Increases in plasma exposure to bedaquiline would be expected when it is co-administered with other ritonavir-boosted HIV protease inhibitors. There are currently no data to support a lowered bedaquiline dose in case of concomitant use with lopinavir/ritonavir or other ritonavir-boosted HIV protease inhibitors.

Co-administration of bedaquiline and nevirapine in adults did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on co-administration of bedaquiline and other antiretroviral agents in adults co-infected with HIV and multidrug-resistant *Mycobacterium tuberculosis* are not available.

QT-interval prolonging medicines

There is limited information on the potential for a pharmacodynamic interaction between bedaquiline and medicines that prolong the QT interval. In an interaction study of bedaquiline and ketoconazole in adults, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual medicines.

Moxifloxacin may be included in regimens comprising bedaquiline; the combination has generally been well tolerated. However, in general an additive or synergistic effect on QT prolongation of bedaquiline may occur when co-administered with other medicines that prolong the QT interval and frequent monitoring is recommended (see section 4.4).

QT interval and concomitant clofazimine use

In an open-label trial, mean increases in QTcF were larger in the 17 adults who were using concomitant clofazimine at week 24 (mean change from reference of 31.9 ms) than in subjects who were not using concomitant clofazimine at week 24 (mean change from reference of 12.3 ms) (see section 4.4).

In another study, additive increases in QTcF were observed when combining clofazimine and levofloxacin with bedaquiline.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

There are limited data on the use of bedaquiline in pregnant women. The use of bedaquiline in pregnancy is associated with infants born with lower weight than infants whose mothers did not take bedaquiline; however, these infants did not appear to suffer any late adverse effects.

Animal studies do not indicate direct or indirect reproductive toxicity (see section 5.3).

[TB395 trade name] should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

Bedaquiline passes into breast milk. Limited information suggests that the concentration of bedaquiline is higher in milk than in maternal plasma; this is consistent with animal studies (see section 5.3). Also, there is indication that bedaquiline exposure in breast-fed infants reaches a level similar to that in the mother being treated with bedaquiline.

Because of the potential for adverse reactions in breast-fed infants, a decision must be made whether to discontinue breast-feeding or to discontinue or interrupt bedaquiline therapy, taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Fertility

No human data on the effect of bedaquiline on fertility are available. In female rats, there was no effect on mating or fertility with bedaquiline treatment; however, some effects occurred in male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Bedaquiline may have a minor influence on the ability to drive and use machines. Dizziness has been reported in some patients taking bedaquiline and should be considered when assessing a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions (affecting more than 10% of patients) during treatment with bedaquiline were QT prolongation (61%), nausea (54%), vomiting (54%), arthralgia (45%), raised liver enzyme values (30%), dizziness (18%) and headache (17%).

Tabulated list of adverse reactions

Adverse reactions to [TB395 trade name] are listed below by system organ class (SOC) and frequency. Frequency categories are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10) and uncommon (1 in 1000 to 1 in 100).

Nervous system disorders

Very common	headache, dizziness

Cardiac disorders

Very common	QT interval prolongation

Gastrointestinal disorders

Very common	nausea, vomiting
Common	diarrhoea

Hepatobiliary disorders

Very common	raised liver enzyme values

Musculoskeletal and connective tissue disorders

Very common	arthralgia
Common	myalgia

Other side effects

The following side effects have also been reported with bedaquiline:

- haemoptysis
- chest pain
- anorexia
- rash

Description of selected adverse reactions

QT prolongation

In clinical studies with bedaquiline in adult patients with tuberculosis, mean QTcF increases of less than 10 ms were observed throughout treatment, attributable to M2, the major bedaquiline metabolite. A prolongation of the QTc interval not more than additive was observed when bedaquiline was used in combination with other QT-prolonging drugs (e.g. clofazimine, delamanid, or fluoroquinolones) (see section 4.5). QTcF decreased gradually after the end of bedaquiline treatment.

Raised liver enzyme values

In a study, transaminase elevations of at least 3 times the upper limit of normal developed more frequently in the bedaquiline treatment group than in the placebo group (11/101 [10.9%] versus 6/104 [5.8%]). In the bedaquiline group, most of these increases occurred throughout the 24 weeks of treatment and were reversible.

In another study increases in transaminases were more frequent during longer treatment (40 weeks) with bedaquiline and background regimen, but occurred at the same rate (29.9%) as in the active control group (29.2%). The control treatment consisted of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid, and prothionamide in the first 16 weeks (intensive phase).

Paediatric population

The safety assessment of bedaquiline is based on data from 30 paediatric patients at least 5 years of age with confirmed or probable MDR-TB infection (see section 5.1).

Overall, there was no indication of any differences in the safety profile in 15 adolescents aged from 14 years up to 18 years compared to the adult population.

In 15 patients aged from 5 years up to 11 years, the most common adverse reactions were related to raised liver enzymes (5/15, 33%), reported as ALT/AST increased and hepatotoxicity; hepatotoxicity led to discontinuation of bedaquiline in 3 patients. Liver enzyme values returned to normal after treatment with bedaquiline and background regimen was stopped. Among these 15 paediatric patients, no deaths occurred during treatment with bedaquiline.

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

Intentional or accidental acute overdose with bedaquiline was not reported during clinical trials. In a study in 44 healthy adults receiving a single 800 mg dose of bedaquiline, adverse reactions were consistent with those observed in clinical studies at the recommended dose.

There is no experience of treating acute overdose with [TB395 trade name]. General measures to support basic vital functions including monitoring of vital signs and electrocardiogram (QT interval) should be undertaken for deliberate or accidental overdose. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, ATC code: J04AK05

Mechanism of action

Bedaquiline is a diarylquinoline. Bedaquiline inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an essential enzyme for generating energy in *Mycobacterium tuberculosis*. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

Pharmacodynamic effects

Bedaquiline is active against *M. tuberculosis* with a minimal inhibitory concentration (MIC) for drug-sensitive as well as drug-resistant strains (multi-drug resistant including pre-extensively drug-resistant strains, extensively drug-resistant strains) in the range ≤ 0.008–0.25 mg/L.

In the mouse model for TB infection, bedaquiline has bactericidal and sterilizing activities.

Bedaquiline is bacteriostatic for many non-tuberculous mycobacterial species. However, *M. xenopi*, *M. novocastrense*, *M. shimoidei, M. flavescens* and non-mycobacterial species are considered inherently resistant to bedaquiline.

Pharmacokinetic/pharmacodynamic relationship

At therapeutic doses, no pharmacokinetic/pharmacodynamic relationship was observed in patients.

Mechanisms of resistance

Acquired resistance mechanisms that affect bedaquiline MICs include mutations in the *atpE* gene, which codes for the ATP synthase target, and in the *Rv0678* gene, which regulates the expression of the MmpS5-MmpL5 efflux pump. Target-based mutations generated in preclinical studies lead to 8- to 133-fold increases in bedaquiline MIC, resulting in MICs ranging from 0.25 to 4 mg/L. Efflux-based mutations have been seen in preclinical and clinical isolates. These lead to 2- to 8-fold increases in bedaquiline MICs, resulting in bedaquiline MICs ranging from 0.25 to 0.5 mg/L. The majority of isolates that are phenotypically resistant to bedaquiline are cross-resistant to clofazimine. Isolates that are resistant to clofazimine can still be susceptible to bedaquiline.

The impact of high baseline bedaquiline MICs, the presence of *Rv0678* based mutations at baseline, or increased post-baseline bedaquiline MICs on microbiologic outcomes is unclear because such cases have been rare in clinical trials.

Susceptibility testing breakpoints

When available, the clinical microbiology laboratory should provide the susceptibility test results for antimicrobial medicines used in resident hospitals as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid in selecting a combination of antibacterial medicines for treatment.

Breakpoints

Minimal inhibitory concentration (MIC) breakpoints are as follows:

Epidemiological cut-off (ECOFF)	0.25 mg/L
Clinical Breakpoints	Susceptible ≤ 0.25 mg/L; Resistant > 0.25 mg/L

Commonly susceptible species

- *Mycobacterium tuberculosis*

Inherently resistant organisms

- *Mycobacterium xenopi*
- *Mycobacterium novocastrense*
- *Mycobacterium shimoidei*
- *Mycobacterium flavescens*
- Non-mycobacterial species

Clinical efficacy and safety

A Phase IIb, placebo-controlled, double-blind, randomised trial evaluated the antibacterial activity, safety, and tolerability of bedaquiline in newly diagnosed adults with sputum smear-positive pulmonary tuberculosis due to *M. tuberculosis* resistant to at least rifampicin and isoniazid, including patients with resistance to second-line injectables or fluoroquinolones. Patients received bedaquiline (N=79) or placebo (N=81) for 24 weeks, both in combination with a preferred 5-drug background regimen (BR) consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone.

Bedaquiline was administered as 400 mg once daily for the first 2 weeks, and as 200 mg 3 times each week for the following 22 weeks.

Time to sputum culture conversion (i.e. the interval between the first bedaquiline dose and the first of two consecutive negative liquid cultures from sputum collected at least 25 days apart) during treatment was 83 days for the bedaquiline group and 125 days for the placebo group (hazard ratio, 95% CI: 2.44 [1.57; 3.80]), $p < 0.0001$).

During the trial, 12.7% (10/79) of the patients died in the bedaquiline treatment group (N=79) compared to 3.7% (3/81) of the patients in the placebo group (N=81). One death occurred during administration of bedaquiline. The median time to death for the remaining nine patients was 344 days after last intake of bedaquiline. In the bedaquiline treatment group, the most common cause of death as reported by the investigator was tuberculosis (5 patients). The causes of death in the remaining patients treated with bedaquiline varied.

Another study evaluated the safety, tolerability, and efficacy of 24 weeks treatment with open-label bedaquiline as part of an individualised treatment regimen in 233 adult patients with sputum smear-positive drug-resistant tuberculosis.

The primary efficacy endpoint was the time to sputum culture conversion during treatment with bedaquiline (median 57 days for 205 patients with sufficient data). At week 24, sputum culture conversion was seen in 163/205 (79.5%) patients. At week 120, sputum culture conversion was seen in 148/205 (72.2%) patients. At week 24 and week 120, responder rates were higher for patients on 3 or more active substances (in vitro) in their background regimen.

Sixteen patients (6.9%) died. The most common cause of death as reported by the investigator was tuberculosis (9 patients). All but one patient who died of tuberculosis had not converted or had relapsed. The causes of death in the remaining patients varied.

STREAM Stage 2 was a Phase III, open-label, multicentre, active-controlled, randomised trial in patients with sputum smear-positive pulmonary drug-resistant tuberculosis. It evaluated non-inferiority of an all-oral bedaquiline-containing treatment regimen (Group C) to a control regimen without bedaquiline (Group B):

- Group B (N=202), a 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid, and prothionamide in the first 16 weeks (intensive phase)
- Group C (N=211), a 40-week, all-oral treatment of bedaquiline, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)

Bedaquiline was administered as 400 mg once daily for the first 2 weeks, and 200 mg 3 times/week for the following 38 weeks. Changes in treatment regimen were permitted at the discretion of the investigator in all groups.

The primary efficacy outcome measure was the proportion of patients with a favourable outcome at Week 76. A favourable outcome was defined as last 2 consecutive cultures negative and no unfavourable outcome. An unfavourable outcome encompassed clinically relevant changes in treatment, all-cause mortality, at least 1 of the last 2 culture results positive, or no culture results within the Week 76 window. The results are shown in the table below.

	mITT population	
	Bedaquiline-regimen (Group C; n=196)	Control-regimen (Group B; n=187)
Favourable outcome at Week 76	82.7%	71.1%
unfavourable outcome at Week 76	17.3%	28.9%
Reasons for unfavourable outcome through Week 76[a]		
Treatment modified or extended	8.2%	23.0%
No culture results within Week 76 window	6.1%	3.7%
Death through Week 76	2.6%	1.1%
At least one of last 2 cultures positive at Week 76	0.5%	1.1%

mITT = modified intent-to-treat

[a] Patients were classified by the first event that made the patient unfavourable. Of the patients with an unfavourable outcome at Week 76 in the control group, 29 patients had a treatment modification from their allocated treatment that included bedaquiline as part of a salvage regimen.

The frequency of deaths was similar across treatment groups through Week 132. In the group treated with the bedaquiline regimen, 11/211 (5.2%) patients died; the most common cause of death was related to tuberculosis (5 patients). In the group treated with the control-regimen, 8/202 (4.0%) patients died, including 4 of 29 patients who received bedaquiline as part of a salvage treatment; the most common cause of death was related to respiratory pathology. The adjusted difference in proportion of fatal adverse events between the 40-week bedaquiline group and the 40-week active control group was 1.2% [95% CI (-2.8%; 5.2%)].

Paediatric population

The pharmacokinetics, safety, and tolerability of bedaquiline in combination with a background regimen were evaluated in a single-arm, open-label, multi-cohort Phase II trial in 30 patients with confirmed or probable MDR-TB infection.

Paediatric patients (12 years up to 18 years of age)

Fifteen patients with a median age of 16 years (range: 14–17 years), weighed 38 to 75 kg, and were 80% female, 53.3% Black and 13.3% Asian. The patients were to complete at least 24 weeks of treatment with bedaquiline administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times a week for the following 22 weeks.

In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with a regimen that included bedaquiline resulted in conversion to a negative culture in 75% (6/8 microbiologically evaluable patients) at week 24.

Paediatric patients (5 years up to 12 years of age)

Fifteen patients with a median age of 7 years (range: 5–10 years), weighed 14 to 36 kg, and were 60% female, 60% Black, 33% White and 7% Asian. The patients were to complete at least 24 weeks of treatment with bedaquiline 200 mg once daily for the first 2 weeks and 100 mg 3 times a week for the following 22 weeks.

In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with a regimen that included bedaquiline resulted in conversion to a negative culture in 100% (3/3 microbiologically evaluable patients) at week 24.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB395 trade name] have been determined in healthy subjects under fed conditions as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**
	Bedaquiline
Maximum concentration (Cmax) ng/mL	1360 ± 433
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL	18774 ± 5392
Time to attain maximum concentration (T_{max}) hour	5.00 (3.00 – 6.50)

Pharmacokinetics of bedaquiline

General	
	The pharmacokinetics of bedaquiline have been evaluated in healthy adults and in multi-drug resistant tuberculosis-infected patients 5 years and older. Exposure to bedaquiline was lower in multi-drug resistant tuberculosis-infected patients than in healthy subjects.
Absorption	
Absolute bioavailability	Not available
Food effect	Bioavailability increases 2-fold when bedaquiline is taken with food compared to administration under fasting conditions
T_{max}	5 hours
Distribution	
Volume of distribution (mean)	Approximately 164 L (Vc)
Plasma protein binding in vitro	> 99.9% Plasma protein binding of the *N*-monodesmethyl metabolite (M2) is at least 99.8%
Tissue distribution	Bedaquiline and the M2 metabolite are extensively distributed in most tissues with the exception of brain, in which uptake is low
Metabolism	
	Mainly hepatic CYP3A4
Active metabolites	*N*-monodesmethyl bedaquiline (4–6 times less active in terms of antimycobacterial potency)
Elimination	

Terminal elimination half-life	About 5 months for both bedaquiline and the M2 metabolite (range 2 to 8 months)
% of dose excreted in urine	<0.001% as unchanged drug
% of dose excreted in faeces	Majority of administered dose
Pharmacokinetic linearity	
	Exposure increases linearly up to the highest doses studied (700-mg single dose and once-daily 400-mg multiple doses)
Drug interactions (in vitro)	
	Bedaquiline does not significantly inhibit the activity of any of the CYP450 enzymes tested (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5 and CYP4A)
	Bedaquiline does not induce CYP1A2, CYP2C9 or CYP2C19 activity.
	Bedaquiline and M2 were not substrates of P-gp in vitro. Bedaquiline was a weak OCT1, OATP1B1 and OATP1B3 substrate in vitro, while M2 was not. Bedaquiline was not a substrate of MRP2 and BCRP in vitro. Bedaquiline and M2 did not inhibit the transporters P-gp, OATP1B1, OATP1B3, BCRP, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2 at clinically relevant concentrations in vitro. An in vitro study indicated a potential for bedaquiline to inhibit BCRP at the concentrations achieved in the intestine after oral administration. The clinical relevance is unknown.

Special populations

Renal impairment

In a population pharmacokinetic analysis of patients with tuberculosis treated with bedaquiline 200 mg 3 times a week, creatinine clearance (range: 40 to 227 mL/minute) did not influence the pharmacokinetic parameters of bedaquiline.

In patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis, bedaquiline concentrations may be increased due to alteration of active substance absorption, distribution, and metabolism secondary to renal dysfunction.

As bedaquiline is highly bound to plasma proteins, it is unlikely to be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic impairment

A single-dose study of bedaquiline in 8 subjects with moderate hepatic impairment (Child-Pugh B) showed that exposure to bedaquiline and M2 (AUC_{672h}) was 19% lower compared to healthy subjects. Bedaquiline has not been studied in patients with severe hepatic impairment.

Paediatric patients

In paediatric patients aged 5 years up to 18 years and weighing 15 to 30 kg, the average plasma exposure of bedaquiline (AUC_{168h}) at week 24 is predicted to be 152 µg·hour/mL (90% prediction interval: 54.3–313 µg·hour/mL) when treated with the recommended weight-based dosing regimen.

In paediatric patients weighing from 30 to 40 kg, the average plasma exposure of bedaquiline (AUC_{168h}) at week 24 is predicted to be higher (average: 229 µg·hour/mL; 90% prediction interval: 68–484 µg·hour/mL) compared to adult patients.

In paediatric patients aged 5 years up to 18 years and weighing over 40 kg, the average plasma exposure of bedaquiline (AUC_{168h}) at week 24 is predicted to be 165 µg·hour/mL (90% prediction interval: 51.2–350 µg·hour/mL) when treated with the recommended weight-based dosing regimen.

The average plasma exposure of bedaquiline (AUC_{168h}) at week 24 in adults was predicted to be 127 µg·hour/mL (90% prediction interval: 39.7–249 µg·hour/mL).

The pharmacokinetics of bedaquiline in paediatric patients less than 5 years of age or weighing less than 15 kg have not been established.

Elderly patients

The limited available data on the use of bedaquiline in tuberculosis patients aged 65 years and older does not suggest an influence of older age on the pharmacokinetics of bedaquiline.

Race

In a population pharmacokinetic analysis of patients with tuberculosis treated with bedaquiline, exposure to bedaquiline was found to be lower in Black patients than in patients from other race categories. This low exposure was not considered clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials. Furthermore, response rates in patients that completed bedaquiline treatment were comparable between different race categories in the clinical trials.

5.3 Preclinical safety data

Animal toxicology studies have been conducted with bedaquiline administration up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. The plasma bedaquiline exposure (AUC) in rats and dogs was similar to that in humans. Bedaquiline was associated with effects in target organs which included monocytic phagocytic system (MPS), skeletal muscle, liver, stomach, pancreas and heart muscle. All these toxicities, except effects on MPS, were monitored clinically. In the MPS of all species, pigment-laden and/or foamy macrophages were also seen in various tissues, consistent with phospholipidosis. The significance of phospholipidosis in humans is unknown. Most of the observed changes occurred after prolonged daily dosing and subsequent increases in plasma and tissue concentrations of the active substance. After stopping treatment, all indications of toxicity exhibited at least partial recovery to good recovery.

In rats, bedaquiline at the high doses of 10 mg/kg daily in females and 20 mg/kg daily in males, did not increase the incidence of any treatment-related tumour. Compared to patients treated with bedaquiline, the exposure (AUC) in female rats was similar and 2-fold higher in male rats; the exposure for the metabolite M2 was 2-fold higher in female rats and 3-fold higher in male rats.

Non-clinical data reveal no specific hazard for humans based on conventional studies for genotoxicity and carcinogenic potential.

Bedaquiline had no effects on fertility in female rats. Three of 24 male rats treated with high bedaquiline doses failed to produce offspring in the fertility study. Normal spermatogenesis and a normal amount of spermatozoa in the epididymides were noted in these animals. No structural abnormalities in the testes and epididymides were seen after up to 6-months of bedaquiline treatment.

No relevant bedaquiline-related effects on developmental toxicity parameters were observed in rats and rabbits. The corresponding plasma exposure (AUC) was 2-fold higher in rats compared to humans. In the rat, no adverse effects were observed in a pre- and post-natal development study at maternal plasma exposure (AUC) similar to humans and exposure in the offspring 3-fold higher than in adult humans. There was no effect of maternal treatment with bedaquiline at any dose level on sexual maturation, behavioural development, mating performance, fertility or reproductive capacity of the F1 generation animals.

Body weight decreases in pups were noted in high-dose groups during the lactation period after exposure to bedaquiline via milk and were not a consequence of in utero exposure. Concentrations of bedaquiline in milk were 6- to12-fold higher that the maximum concentration in maternal plasma.

In a juvenile rat toxicity study, the no observed adverse effect level (NOAEL) was 15 mg/kg/day (maximum dose 45 mg/kg/day) for observations of diffuse inflammation and/or degeneration in skeletal muscle (reversible), oesophagus (reversible) and tongue (reversible), liver hypertrophy (reversible) and corticomedullary renal mineralisation (partial recovery in males, and no recovery in females within 8 weeks after end of exposure). The NOAEL corresponds to a plasma AUC_{24h} of 13.1 and 35.6 µg·hour/mL for bedaquiline (about 0.7 times clinical dose) and 10.5 and 16.3 µg·hour/mL for the *N*-monodesmethyl metabolite of bedaquiline (M2) in males and females (about 1.8 times clinical dose), respectively.

Environmental risk assessment

Environmental risk assessment studies have shown that bedaquiline has the potential to be persistent, bioaccumulative and toxic to the environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Hydroxypropyl methylcellulose

Polysorbate

Microcrystalline cellulose

Croscarmellose sodium

Colloidal silicon dioxide

Magnesium stearate

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

In-use period (for HDPE bottles)

Discard the product 90 days after initial opening.

6.4 Special precautions for storage

Do not store above 30°C.

Store tablets in the original container to protect from light.

6.5 Nature and contents of container

HDPE bottles

Round, opaque white plastic (HDPE) bottle containing 188 tablets. The bottle has an aluminium/plastic foil seal and a white plastic (polypropylene) child resistant cap.

Blister packs

Aluminium foil on aluminium foil blister cards, each containing 6 or 10 tablets. Available in packs of 4 x 6, 1 x 10, 3 x 10, 10 x 10 tablets.

6.6 Special precautions for disposal and other handling

Extemporaneous preparation for children weighing less than 16 kg

If a suitable formulation is not available, an extemporaneous preparation may be made mixing one bedaquiline 100 mg tablet in 10 mL water. The caregiver should be instructed on how to prepare the mixture as follows:

For preparing the liquid mixture for children weighing less than 16 kg you need:

- Two small cups
- a teaspoon
- drinking water

- a 10-mL oral syringe, showing measurements of 1.0 mL.

The following steps should be followed:

1. Crush one bedaquiline 100 mg tablet in the first small cup.
2. Measure out 10 mL drinking water using the syringe and add it to the first cup.
3. Stir well until all the crushed tablet is fully mixed, taking care not to spill any of the mixture.
4. Look up the patient's weight and age in the above table (first 2 columns).
5. Then look under 'How much mixture to give', to find the right dose for the child.
6. Use the syringe to draw up the correct amount of liquid mixture from the first cup and make sure there are no bubbles in the mixture you have drawn up.
7. Transfer the mixture to the second cup (or a bottle for an infant) and give it to the child straight away.
8. If there is anything left in the second cup, rinse the cup with a small amount of water and get the child to drink it all. Use a spoon (or a bottle for an infant) to give the child the remaining mixture. This is to make sure that the child gets the full dose.
9. Give the child something to drink after taking the medicine.
10. Throw away any liquid left in the first cup.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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TB395

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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Section 6 was updated in July 2025.

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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