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

[TB396 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 153mg of lactose monohydrate. See section 4-4.

For the full list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM

Tablets

White to off-white, round, uncoated tablets. They are biconvex (rounded on top and bottom). The tablets are plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB396 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 [TB396 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 [TB396 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.

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

Adults and adolescents at least 14 years old

First 8 weeks	bedaquiline 200 mg (2 tablets of [TB396 trade name]) **once daily**
Week 9 onwards	bedaquiline 100 mg (1 tablet of [TB396 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.

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 [TB396 trade name]) **once daily**
Week 3 onwards	bedaquiline 200 mg (2 tablets of [TB396 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 [TB396 trade name]) **once daily**
Week 3 onwards	bedaquiline 100 mg (1 tablet of [TB396 trade name]) once daily for **3 days each week** (for example, on Mondays, Wednesdays, and Fridays)

Missed doses

If the patient misses a dose of [TB396 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 [TB396 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 [TB396 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 [TB396 trade name] is interrupted for more than 2 weeks (but less than 8 weeks) because of side effects, the patient should take the initial higher daily dose for 7 days before recommencing the lower dose on 3 days each week.

Elderly

There are limited clinical data on the use of [TB396 trade name] in elderly patients.

Infants and young children

The safety and efficacy of [TB396 trade name] have not been established in children younger than 14 years for the 6-month regimens.

The safety and efficacy of [TB396 trade name] have not been established in children weighing less than 16 kg for the 9-month (or longer) regimens.

Hepatic impairment

No dose adjustment is necessary for [TB396 trade name] in patients with mild or moderate hepatic impairment (see section 5.2). [TB396 trade name] should be used with caution in patients with moderate hepatic impairment (see section 5.2). [TB396 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, [TB396 trade name] should be used with caution (see section 5.2).

Method of administration

[TB396 trade name] should be taken with food, because food increases bioavailability by about 2-fold (see section 5.2). [TB396 trade name] tablets should be swallowed whole with water.

For patients not able to swallow the tablets whole, the tablets may be crushed and suspended in a small amount of drinking water in a clean cup. The mixture should be vigorously stirred before being swallowed immediately, and the cup rinsed with a further small amount of water, which should also be swallowed to ensure all the dose is taken.

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:

1. extra-pulmonary tuberculosis (e.g. central nervous system, bone)
2. infections due to mycobacterial species other than *Mycobacterium tuberculosis*
3. 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).

[TB396 trade name] treatment is not recommended in patients with the following, unless the benefits of bedaquiline are considered to outweigh the potential risks:

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

[TB396 trade name] must be discontinued if the patient develops:

1. Clinically significant ventricular arrhythmia
2. 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 [TB396 trade name] and/or any hepatotoxic background medicine should be discontinued.

Other hepatotoxic medicines and alcohol should be avoided while on [TB396 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

This medicine contains **lactose**. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The small amount of lactose in a dose may 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

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 should be avoided 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*). 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 should be avoided of bedaquiline and moderate or strong CYP3A4 inhibitors (e.g. ciprofloxacin, clarithromycin, erythromycin, fluconazole, ketoconazole, ritonavir) given for more than 14 consecutive days. This is because prolonged use of CYP3A4 inhibitors can increase bedaquiline levels and therefore its side effects. If co-administration with such CYP3A4 inhibitors is necessary, more frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.4).

Short-term co-administration of bedaquiline and ketoconazole (a potent CYP3A4 inhibitor) in healthy adults increased bedaquiline's exposure (AUC) by around 20%. 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 multi-drug 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%. A more pronounced effect on bedaquiline plasma exposures may occur during prolonged co-administration with lopinavir/ritonavir. Published data on adults treated with bedaquiline as part of therapy for drug-resistant tuberculosis and lopinavir/ritonavir-based treatment have shown that bedaquiline exposure over 48 hours increased about 2-fold. This increase is likely due to ritonavir. If the benefit outweighs the risk, [TB396 trade name] may be used with caution with lopinavir/ritonavir. Increases in plasma exposure to bedaquiline would be expected when it is co-administered with other ritonavir-boosted HIV protease inhibitors. Of note, no change in bedaquiline dosing is recommended for co-treatment with lopinavir/ritonavir or other ritonavir-boosted HIV protease inhibitors. There are no data to support a lowered bedaquiline dose in such circumstances.

Co-administration of single-dose bedaquiline and multiple-dose nevirapine in adults did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on co-administration of bedaquiline and antiretroviral agents in adults co-infected with HIV and multi-drug resistant *Mycobacterium tuberculosis* are not available (see section 4.4). Efavirenz is a moderate inducer of CYP3A4 activity; co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity, and is, therefore, not recommended.

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).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

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).

[TB396 trade name] should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding

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 breastfed 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

Adverse reactions for bedaquiline were identified from pooled Phase IIb clinical trial data from 335 adult patients who received bedaquiline in combination with a background regimen of tuberculosis medicines. The

assessment of causality was also based on a review of the pooled Phase I and Phase IIa safety data in adults. The most frequent adverse drug reactions (affecting more than 10% of patients) during treatment with bedaquiline were nausea (35.3% in the bedaquiline group vs 25.7% in the placebo group), arthralgia (29.4% vs 20.0%), headache (23.5% vs 11.4%), vomiting (20.6% vs 22.9%) and dizziness (12.7% vs 11.4%).

Tabulated list of adverse reactions

Adverse reactions to [TB396 trade name] from controlled trials in 102 adult patients treated with bedaquiline are presented in the table below.

Adverse drug reactions are listed 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	
Common	QT interval prolongation
Gastrointestinal disorders	
Very common	nausea, vomiting
Common	diarrhoea
Hepatobiliary disorders	
Common	raised transaminases; raised AST, ALT and hepatic enzyme; abnormal hepatic function
Musculoskeletal and connective tissue disorders	
Very common	arthralgia
Common	myalgia

Other side effects

The following side effects have also been reported with bedaquiline:

1. haemoptysis
2. chest pain
3. anorexia
4. rash

Description of selected adverse reactions

Cardiovascular

In a controlled Phase IIb study, mean QTcF values increased from baseline from the first on-treatment assessment onwards (9.9 ms at week 1 for bedaquiline and 3.5 ms for placebo). The largest mean increase from baseline values in QTcF during the 24 weeks of bedaquiline treatment was 15.7 ms (at week 18). The largest mean increase from baseline values in QTcF in the placebo group was 6.2 ms (also at week 18) (see section 4.4). After the end of bedaquiline treatment (i.e. after week 24), QTcF increases in the bedaquiline group gradually became less pronounced.

In a Phase IIb, open label study, where patients with no treatment options received other QT-prolonging medicines for treating tuberculosis, including clofazimine, concurrent use with bedaquiline resulted in additive QT prolongation, proportional to the number of QT prolonging medicines in the treatment regimen.

Patients receiving bedaquiline alone with no other QT-prolonging medicine developed a maximal mean QTcF increase over baseline of 23.7 ms with no QT duration in excess of 480 ms, whereas patients with at least 2 other QT-prolonging medicines developed a maximal mean QTcF prolongation of 30.7 ms over baseline, resulting in a QTcF duration exceeding 500 ms in one patient.

There were no cases of torsade de pointes in the safety database (see section 4.4). See section 4.5 'QT interval and concomitant clofazimine use' for further information regarding patients using clofazimine concomitantly.

Increased transaminases

In a study, aminotransferase elevations of at least 3 times the upper limit of normal developed more frequently in the bedaquiline treatment group than in the placebo group (11/102 [10.8%] versus 6/105 [5.7%]). In the bedaquiline group, most of these increases occurred throughout the 24 weeks of treatment and were reversible. During the study's investigational phase, raised aminotransferases was reported in 7/79 (8.9%) patients in the bedaquiline group compared to 1/81 (1.2%) in the placebo group.

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. Elevations in liver enzymes were reversible on discontinuing bedaquiline and background regimen. 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 [TB396 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 ≤ 0.008–0.12 mg/L. The *N*-monodesmethyl metabolite (M2) is not thought to contribute significantly to clinical efficacy given its lower average exposure (23 to 31%) in humans and lower antimycobacterial activity (3- to 6-fold lower) compared to the parent compound.

The intracellular bactericidal activity of bedaquiline in primary peritoneal macrophages and in a macrophage-like cell line was greater than its extracellular activity. Bedaquiline is also bactericidal against dormant (non-replicating) tubercle bacilli. 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* 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 the Phase II 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

1. *Mycobacterium tuberculosis*

Inherently resistant organisms

2. *Mycobacterium xenopi*
3. *Mycobacterium novocastrense*
4. *Mycobacterium shimoidei*
5. Non-mycobacterial species

Clinical efficacy and safety

The following definitions apply for resistance categories used:

Multi-drug resistant *M. tuberculosis* ($MDR_{H\&R}$-TB)	isolate resistant to at least isoniazid and rifampicin, but susceptible to fluoroquinolones and second-line injectable agents
Pre-extensively drug-resistant tuberculosis (pre-XDR-TB)	isolate resistant to isoniazid, rifampicin, and either any fluoroquinolone or at least one second-line injectable agent (but not to both a fluoroquinolone and a second-line injectable agent)
Extensively drug-resistant tuberculosis (XDR-TB)	isolate resistant to isoniazid, rifampicin, any fluoroquinolone, and at least one second line injectable agent

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 $MDR_{H\&R}$-TB and pre-XDR-TB. Patients received bedaquiline (n = 79) or placebo (n = 81) for 24 weeks, both in combination with a preferred 5-drug background regimen of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone. After the 24-week period, the background regimen was continued to complete 18 to 24 months of total multi-drug resistant *M. tuberculosis* treatment. A final evaluation was conducted at week 120. Main demographics were as follows: 63.1% were males, median age 34 years, 35% were Black, and 15% were HIV positive. Cavitation in one lung was seen in 58% of patients, and in both lungs in 16%. For patients with full characterisation of resistance status, 76% (84/111) were infected with an $MDR_{H\&R}$-TB strain and 24% (27/111) with a pre-XDR-TB strain.

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.

The primary outcome parameter was the 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 with bedaquiline or placebo (median time to conversion was 83 days for the bedaquiline group, 125 days for the placebo group (hazard ratio, 95% CI: 2.44 [1.57; 3.80]), $p < 0.0001$).

In the bedaquiline group, no or only minor differences in time to culture conversion and culture conversion rates were observed between patients with pre-XDR-TB and patients with $MDR_{H\&R}$-TB.

Response rates at week 24 and week 120 (i.e. around 6 months after stopping all therapy) are presented in table 2:

Culture conversion status				
Culture conversion status, n (%)	**mITT population**			
	n	Bedaquiline + background regimen	n	Placebo + background regimen
Overall responder at week 24	66	52 (78.8%)	66	38 (57.6%)
Patients with $MDR_{H\&R}$-TB	39	32 (82.1%)	45	28 (62.2%)
Patients with pre-XDR-TB	15	11 (73.3%)	12	4 (33.3%)
Overall non-responder* at week 24	66	14 (21.2%)	66	28 (42.4%)
Overall responder at week 120	66	41 (62.1%)	66	29 (43.9%)
Patients with $MDR_{H\&R}$-TB	39[#]	27 (69.2%)	46[# §]	20 (43.5%)
Patients with pre-XDR-TB	15[#]	9 (60.0%)	12[#]	5 (41.7%)
Overall non-responder at week 120	66	25 (37.9%)	66	37 (56.1%)

Failure to convert	66	8 (12.1%)	66	15 (22.7%)
Relapse**	66	6 (9.1%)	66	10 (15.2%)
Discontinued but converted	66	11 (16.7%)	66	12 (18.2%)

* Patients who died during the trial or discontinued the trial were considered as non-responders.

** Relapse was defined as having a positive sputum culture after **or during** treatment, following prior sputum conversion.

Extent of resistance based on laboratory drug susceptibility testing results was not available for 20 patients in the mITT population (12 in the bedaquiline group and 8 in the placebo group). These patients were excluded from the subgroup analysis by extent of resistance of *M. tuberculosis* strain.

§ Central laboratory drug susceptibility testing results became available for one additional placebo subjects after the Week 24 interim analysis.

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 who were sputum smear positive within 6 months prior to screening. This study included patients of all resistance categories ($MDR_{H\&R}$-TB, pre-XDR-TB and XDR-TB).

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. Conversion rates at week 24 were highest (87.1%; 81/93) in patients with $MDR_{H\&R}$-TB, 77.3% (34/44) in pre-XDR-TB patients and lowest (54.1%; 20/37) in XDR-TB patients. Extent of resistance based on laboratory drug susceptibility testing results was not available for 32 subjects in the mITT population. These subjects were excluded from the subgroup analysis by extent of resistance of *M. tuberculosis* strain.

At week 120, sputum culture conversion was seen in 148/205 (72.2%) patients. Conversion rates at week 120 were highest (73.1%; 68/93) in patients with $MDR_{H\&R}$-TB, 70.5% (31/44) in pre-XDR-TB patients and lowest (62.2%; 23/37) in XDR-TB 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.

Of the 163 patients who were responders at week 24, 139 patients (85.3%) were still responders at week 120. Twenty-four of these 24-week responders (14.7%) were considered non-responders at week 120, of which 19 patients had prematurely discontinued the trial while being culture converted and 5 patients had experienced relapse. Of the 42 patients who were non-responders at week 24, confirmed culture conversion after week 24 (i.e. after bedaquiline dosing ended but the background regimen was continued) occurred in 9 patients (21.4%) and was maintained at week 120.

Mortality

In the randomised phase IIb study a higher rate of death was seen in the bedaquiline treatment group (12.7%; 10/79 patients) compared to the placebo treatment group (3.7%; 3/81 patients). One death in the bedaquiline group and one death in the placebo group were reported after the week 120 window. In the bedaquiline group, all of the 5 deaths due to tuberculosis occurred in patients whose sputum culture status at last visit was 'not converted'. The causes of death in the remaining bedaquiline patients were alcohol poisoning, hepatitis/hepatic cirrhosis, septic shock/peritonitis, cerebrovascular accident and motor vehicle accident. One of the ten deaths in the bedaquiline group (due to alcohol poisoning) occurred during the 24-week treatment period. The other 9 deaths among those treated with bedaquiline occurred after completion of treatment with bedaquiline (range 86–911 days after bedaquiline; median 344 days). The imbalance in deaths between the two treatment groups is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other medicines used to treat tuberculosis, human immunodeficiency virus status, or severity of disease could be observed. During the trial, there was no evidence of antecedent significant QT prolongation or clinically significant dysrhythmia in any of the patients that died.

In the Phase IIb, open label study, 6.9% (16/233) patients 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.

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 a 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

Absorption of [TB396 trade name]

The absorption characteristics of [TB396 trade name] have been determined after administration of one bedaqualine 100 mg tablet in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	1040 ± 267 ng/mL
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	13776 ± 3449 ng·h/mL
Time to attain maximum concentration (T_{max})[#]	6.0 (3.0 – 6.0)

*arithmetic mean; [#]median (range)

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 tuberculosis patients 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) demonstrated 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.

Pediatric 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

There are limited clinical data on the use of bedaquiline in tuberculosis patients aged 65 years and older. In a population pharmacokinetic analysis of tuberculosis patients (age range 18 to 68 years) treated with bedaquiline, age did not influence the pharmacokinetics of bedaquiline.

Race

In a population pharmacokinetic analysis of tuberculosis patients 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.

5.1 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

Corn starch
Croscarmellose sodium
Microcrystalline cellulose
Lactose monohydrate
Polysorbate 20
Hypromellose
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

24 months (Blisters; Alu-Alu)
24 months (HDPE Bottle)
30 months (Strips; Alu-Alu)

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container or package to protect from light. Avoid excursions above 30°C.

6.5 Nature and contents of container

Plastic (HDPE) bottles

Round, opaque, white plastic (HDPE) bottle containing 24 or 188 tablets. The bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

Blister packs

Aluminium foil on aluminium foil blister cards, each containing 12 or 14 tablets. Available in cartons of 8 x 12, 11 x 12 or 4 x 14 tablets.

Strip pack

Aluminium foil strip packs, each containing 10 or 14 tablets. Available in boxes of 10 x 10 or 4×14 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

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TB396

9. DATE OF PREQUALIFICATION

16 November 2023

10. DATE OF REVISION OF THE TEXT

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