WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

Bedaquiline 100mg tablet
## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse event reaction</td>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>ATP</td>
<td>Adenosine 5’-triphosphate</td>
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<tr>
<td>BR</td>
<td>Background regimen</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<td>DOT</td>
<td>Directly observed therapy</td>
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<td>DS</td>
<td>Drug-susceptible</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>ETH</td>
<td>Ethionamide</td>
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<tr>
<td>GDF</td>
<td>Stop TB Partnership’s Global Drug Facility</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IDA</td>
<td>International Dispensary Association</td>
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<tr>
<td>INN</td>
<td>International non-proprietary name</td>
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<tr>
<td>KAN</td>
<td>Kanamycin</td>
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<tr>
<td>mITT</td>
<td>Modified intent-to-treat</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant tuberculosis including pre-XDR- and XDR-TB (see “definitions of terms”)</td>
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<tr>
<td>M. tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<td>NTP</td>
<td>National TB program</td>
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<td>OFL</td>
<td>Ofloxacin</td>
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<td>PZA</td>
<td>Pyrazinamide</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<tr>
<td>SOC</td>
<td>Standard of care</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR-TB</td>
<td>Extensively drug-resistant tuberculosis</td>
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1. Summary statement of the proposal for inclusion, change or deletion:

Bedaquiline is indicated in adults ($\geq 18$ years) as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug resistant (MDR) strains of *Mycobacterium tuberculosis*.

The principal reasons for requesting the inclusion of the tablet formulation of bedaquiline 100 mg are as follows:

1. Appropriate treatment of MDR-TB remains a major challenge globally, in particular in high-TB burden countries.
2. Globally, 3.5% of new and 20.5% of previously treated TB cases were estimated to have had MDR-TB in 2013. This translates into an estimated 480 000 people having developed MDR-TB in 2013.
3. On average, an estimated 9.0% of patients with MDR-TB had extensively drug resistant TB (XDR-TB).
4. If all notified TB patients (6.1 million, new and previously treated) had been tested for drug resistance in 2013, an estimated 300 000 cases of MDR-TB would have been detected, more than half of these in three countries alone: India, China and the Russian Federation.
5. In 2013, 136 000 of the estimated 300 000 MDR-TB patients who could have been detected were diagnosed and notified. This was equivalent to almost one in two (45%), and up from one in six in 2009. Progress in the detection of drug-resistant TB has been facilitated by the use of new rapid diagnostics.
6. A total of 97 000 patients were started on MDR-TB treatment in 2013, a three-fold increase compared with 2009. However, 39 000 patients (plus an unknown number detected in previous years) were on waiting lists, and the gap between diagnosis and treatment widened between 2012 and 2013 in several countries.
7. The most recent treatment outcome data are for patients started on MDR-TB treatment in 2011. Globally the success rate was 48%. Only five of the 27 high MDR-TB burden countries achieved a treatment success rate of $\geq 70\%$: Ethiopia, Kazakhstan, Myanmar, Pakistan and Viet Nam. Health system weaknesses, lack of effective regimens and other treatment challenges are responsible for unacceptably low cure rates, and the MDR-TB response is seriously hampered by insufficient funding. These barriers must be urgently addressed.
8. Five priority actions – from prevention to cure – are needed to address the MDR-TB epidemic. These are: 1) high-quality treatment of drug-susceptible TB to prevent MDR-TB; 2) expansion of rapid testing and detection of MDR-TB cases; 3) immediate access to quality care; 4) infection control; and 5) increased political commitment, including adequate funding for current interventions as well as research to develop new diagnostics, drugs and treatment regimens.
9. Bedaquiline is the first drug with a novel mechanism of action for TB in more than 40 years and the first and only one specifically indicated for MDR-TB.
10. The distinct target (ATP synthase inhibition) of bedaquiline ensures the absence of cross-resistance with existing anti-TB drugs.
11. Treatment outcomes of MDR-TB will be improved with the addition of bedaquiline to current treatment regimens.
12. A faster sputum culture conversion and fewer treatment failures resulting from the addition of bedaquiline to second-line drug regimens would significantly reduce the transmission of multidrug-resistant bacteria.


2. **Name of the focal point in WHO submitting or supporting the application:**

3. **Name of the organization(s) consulted and/or supporting the application:**

   Janssen Pharmaceutica N.V.
   Turnhoutseweg 30, Beerse, 2340 Belgium

   JSC Pharmstandard
   Likhachevsky Drive, 5 “B” Moscow
   Dolgoprudny, Russia, 141700

   Contact: Mercè Caturla, Global Regulatory Affairs
   Janssen Infectious Diseases BVBA
   Turnhoutseweg 30, Beerse, 2340 Belgium.

4. **International non-proprietary name (INN, generic name) of the medicine:**

   Bedaquiline

5. **Formulation proposed for inclusion; including adult and pediatric (if appropriate):**

   Adult: Oral tablet: uncoated, white to almost white round biconvex tablet with debossing of "T" over "207" on one side and "100" on the other side.

   Pediatric: Clinical studies on the use of SIRTURO™ in paediatric patients are ongoing.

6. **International availability – sources, if possible manufacturers and trade names:**

   Manufacturer:

   Kemwell Biopharma Pvt. Ltd., Bangalore, India for Janssen Therapeutics, Division of Janssen Products, LP Titusville, NJ 08560 USA

   Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse, 2340 Belgium, has signed a contract with the Stichting International Dispensary Association (IDA), a procurement agent for the Stop TB Partnership's Global Drug Facility (GDF), to facilitate access to bedaquiline.

   Trade name: SIRTURO™
7. Whether listing is requested as an individual medicine or as an example of a therapeutic group:

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

Bedaquiline is a diarylquinoline with in vitro activity against drug-sensitive TB (DS-TB), MDR-TB including pre-extensively drug resistant (pre-XDR-TB) and XDR-TB. Pre-XDR TB is defined as in vitro resistance of the patient’s isolate to: (1) isoniazid, (2) rifampin and (3) either a fluoroquinolone or at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin). XDR-TB is defined as in vitro resistance of the patient’s isolate to: (1) isoniazid, (2) rifampin, (3) a fluoroquinolone and (4) at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

Since bedaquiline is indicated for the treatment of MDR-TB, inclusion within the Complementary List of 6.2.4 Antituberculosis medicines is requested under the statement “Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centers adhering to WHO standards for TB control”.

Due to its novel mode of action, bedaquiline defines a new class of anti-TB compounds; currently, no other drugs belonging to the same pharmacological class as bedaquiline are available.

8. Information supporting the public health relevance:

8.1 Epidemiological information on disease burden

Although the overall incidence of DS-TB that can be treated with first-line drugs has been decreasing over the past two decades, the burden of TB remains high and concentrated within specific high-burden regions1. In 2013, there were 9.0 million incident TB cases, 82% of which occurred in 22 countries. India and China reported the greatest proportion of cases, contributing to around 35% of all incident TB cases globally2.

Similarly, overall mortality rates for TB have decreased by 45% since 1990, however mortality rates remain high in some regions partly due to the coinciding HIV epidemic3. In 2012, 1.5 million deaths occurred globally due to TB (both DS-TB and drug-resistant TB), of which 360 000 were in HIV-infected patients and 80 000 were in children1.

Notification rates of TB infection have increased in recent years due to increasing efforts by the WHO4. Despite this effort, many countries still lack sufficient diagnostic capacity or reporting systems for TB case notification and treatment outcomes. For this reason, notification rates and overall prevalence are assumed to be considerably lower than actual burden and hence estimations are made to account for likely missing data4. As a result, epidemiological data must be interpreted carefully.

MDR-TB cases have been documented in every country surveyed for MDR-TB presence, with 480 000 incident cases emerging annually worldwide4. In 2013, MDR-TB cases were
estimated to account for 5% of all TB cases. An estimated 210 000 deaths occur annually due to MDR-TB\(^1\).

Due to the different mechanisms by which MDR-TB can be acquired, both from primary transmission or development from existing TB, incidence rates of MDR-TB are often reported in two separate groups: treatment-naive/new TB cases and previously treated cases.

Globally, 3.5% of all new TB cases (occurring in treatment-naive patients) are estimated to be MDR-TB, while 20.5% of previously treated TB cases are estimated to be MDR-TB\(^1\). The rates for individual countries will vary, with level of TB control implemented in each region inversely correlated with the proportion of MDR-TB cases that are reported.

The burden of MDR-TB varies greatly by region and the WHO has designated 27 countries as high burden for MDR-TB. Currently, Eastern Europe and the central Asia regions have been identified as having the highest burden of MDR-TB. The top three high burden countries are India, China, and Russia; together these countries held over half of all 300 000 incident MDR-TB cases among notified pulmonary TB cases that emerged in 2013 (range: 230 000-380 000)\(^1\). Approximately 83\% of all incident MDR-TB cases occurred in the 27 high burden countries\(^1\).

MDR-TB incidence in Europe increased at an annual mean rate of 18.6\% between 2007 and 2012\(^10\).

At least one case of XDR-TB has been reported in 100 countries studied to date\(^1\). On average, 9.0\% of all MDR-TB cases in 2013 were found to be XDR-TB (95\% CI, 6.5-11.5), though overall incidence is difficult to estimate due to limited diagnostic capacity\(^1\). Of the countries surveyed, 15 reported more than 10 XDR-TB cases in the most recent year of data availability. The highest levels of XDR-TB from MDR-TB cases have been reported in Georgia (20.0\%), Kazakhstan (22.7\%), Latvia (21.7\%), Lithuania (24.8\%) and Tajikistan (21.0\%)\(^1\).

XDR-TB is more difficult to diagnose, requires complex treatment with drugs that have higher levels of toxicity, is characterized by poor treatment outcomes, and associated with a higher risk of mortality. Strains of XDR-TB evolve from MDR-TB cases using the same mechanism as DS-TB to MDR-TB\(^6\). The risk of XDR-TB is highest in patients with HIV and in individuals who have been treated with second-line TB drugs for a longer period of time than recommended\(^6\).

South Africa remains one of the top-ten high burden MDR-TB countries worldwide, and reports the most XDR-TB cases. Analysis of treatment outcome data has shown that treatment success rates for South Africa are low (just 15\% of patients enrolled on treatment were cured in 2011), with high mortality (40\% in 2011) due to the elevated HIV burden\(^1\). Further, the number of diagnosed XDR-TB cases increased from 467 in 2009 to 1596 in 2012, representing an estimated 10\% of all MDR-TB cases in the country. Nosocomial transmission is a key contributing factor in the spread of MDR- and XDR-TB in South Africa; for example, prevalence of 15\% for MDR-TB and 3\% for XDR-TB among inpatients was recently reported across 19 hospitals in the KwaZulu-Natal province\(^7\).
Recently, TB strains resistant to all known drugs have been reported in Italy, Iran, and India; however, currently there is no validated drug sensitivity testing for all TB drugs due to technical difficulties.

The majority of individuals with MDR-TB are untreated and approximately two-thirds of confirmed cases of MDR-TB are not enrolled on treatment according to international guidelines. For patients with MDR-TB on treatment, treatment success remains low with cure rates typically ranging from 50% to 70%\(^2\), the global success rate is only 48%\(^1\). Only 29 of 126 countries that reported treatment outcomes reached the target treatment success rate of 75% or higher\(^1\).

Death from untreated pulmonary TB is considerable. Ten-year case fatality was estimated in a recent systematic review of studies of the natural history of the disease. Among sputum smear-positive and HIV-negative cases of pulmonary TB, around 70% died within 10 years; among culture-positive (but smear-negative) cases, 20% died within 10 years\(^3\).

Moreover, MDR-TB standard of care is lengthy and costly. For drug-susceptible TB, the regimen lasts 6 months and for MDR-TB, a total treatment duration of 20 months is suggested in WHO guidelines\(^4\). In a recent systematic review of the cost and cost-effectiveness of MDR-TB treatment, the estimated cost of treatment varied from $US 3 401 to $US 195 078 depending on the region and extent of hospitalization or ambulatory care\(^5\).

In a recent analysis of data from the United States of America, three-quarters of patients had to be hospitalised, and direct costs, mostly covered by the public sector, were on average $134 000 per MDR-TB and $430 000 per XDR-TB patient\(^6\). Across a set of 15 high-income countries in the EU, treatment costs for MDR-TB were estimated to average €54 779, rising to €168 310 for XDR-TB\(^9\). Recent data on the cost of MDR-TB patients was recently published, indicating that overall, the average per-patient cost of MDR-TB treatment in low-income countries is $9235, compared with $48 553 in upper middle-income countries. In the WHO high-burden countries, Kenya reported the lowest cost ($2571 per patient), while Russia reported the highest cost ($31 962 per patient)\(^1\). Costs were generally higher in former Soviet Union countries due to more lengthy hospitalizations, which may last up to 180 days (MDR-TB is managed in an inpatient setting in many of these countries rather than an outpatient setting).

\(^1\)WHO. Global Tuberculosis Report 2012.
\(^4\)WHO. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update.
hospital inpatients in KwaZulu Natal, South Africa indicate risk of nosocomial transmission. PLoS Onc. 9(3): e90868


8.2 Assessment of current use

Cumulative Exposure in Clinical Trials
Overall, 400 subjects without tuberculosis, of which 376 were healthy subjects, 8 subjects were hepatic impaired and 16 subjects were human immunodeficiency virus infected; and 516 subjects with tuberculosis have been enrolled in the Company sponsored bedaquiline clinical programme. Up to 5 September 2014, the compassionate use programmes have enrolled 518 subjects and the early access trial has enrolled 57 subjects.

Cumulative and Interval Patient Exposure from Marketing
Based on the total distribution of 5,940.8 g of finished product distributed (from launch to August 2014), the cumulative estimated postmarketing exposure to bedaquiline in all territories is 316 completed treatment courses.

8.3 Target population

Patients (adults ≥18 years) with pulmonary disease caused by MDR-TB, defined as isolates with in vitro resistance to at least isoniazid and rifampin.

9. Treatment details:

9.1 Dosage regimen, duration

Bedaquiline is indicated in adults (≥ 18 years) as part of combination therapy of pulmonary tuberculosis (TB) due to MDR-TB.

Dosage and Administration

Bedaquiline should only be administered as part of a multi-drug resistant tuberculosis (MDR-TB) regimen. It is recommended that bedaquiline is administered by directly observed therapy (DOT). MDR-TB is defined as in vitro resistance of the patient’s isolate to at least isoniazid and rifampicin.

The prescribing physician should refer to WHO and/or national TB treatment guidelines for direction on selection and duration of use of companion drugs. Bedaquiline should only be used in combination with at least 3 drugs to which the patient’s isolate has been shown to be susceptible in vitro. If in vitro drug susceptibility testing results are unavailable, treatment
may be initiated with bedaquiline in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible.

Throughout treatment with, and following the last intake of bedaquiline, patients should continue to take their companion drugs in accordance with national TB treatment guidelines and local MDR-TB treatment practice.

**Dosage – Adults (⩾ 18 years)**
The recommended dosage of bedaquiline for MDR-TB is:

- Weeks 1-2: 400 mg (4 tablets of 100 mg) **once daily**
- Weeks 3-24: 200 mg (2 tablets of 100 mg) **3 times per week** (with at least 48 hours between doses).

The total duration of treatment with bedaquiline is 24 weeks. Bedaquiline should be taken with food.

**Missed dose(s)**
Patients should be advised of the need to take bedaquiline as prescribed. Compliance with the full course of therapy must be emphasized.

If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule.

From Week 3 onwards, if a dose is missed, patients should take the missed dose, and adjust the dosing schedule to ensure the total dose of bedaquiline during the 7 day period does not exceed 600 mg (taken as 3 intakes of 200 mg per day, at least 24 hours apart).

**Special populations**

**Pediatrics (< 18 years of age)**
The safety and efficacy of bedaquiline in children and adolescents less than 18 years of age have not been established.

**Elderly (⩾ 65 years of age)**
There are limited clinical data on the use of bedaquiline in elderly patients.

**Renal impairment**
Bedaquiline has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is insignificant (< 0.001%). No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis, bedaquiline should be used with caution.

**Hepatic impairment**
The pharmacokinetics of bedaquiline were assessed after single-dose administration to subjects with moderate hepatic impairment (Child-Pugh B). Based on these results, no dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic
impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population.

Administration
Bedaquiline should be taken orally with food, as administration with food increases oral bioavailability. It is recommended that the bedaquiline tablet be swallowed whole with water.

9.2 Reference to existing WHO and other clinical guidelines

MDR-TB is TB that is resistant to the two most important first-line drugs: isoniazid and rifampin. For most patients diagnosed with MDR-TB, WHO recommends treatment for 20 months with a regimen that includes second-line anti-TB drugs. WHO Guidelines\(^1\) state:

4.1 In the treatment of patients with MDR-TB, an intensive phase of 8 months is suggested for most patients, and the duration may be modified according to the patient’s response to therapy (conditional recommendation/very low quality evidence)

4.2 In the treatment of patients newly diagnosed with MDR-TB (i.e., not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most patients, and the duration may be modified according to the patient’s response to therapy (conditional recommendation/very low quality evidence).

In 2013, the WHO issued interim policy guidance\(^2\) to provide advice on the inclusion of bedaquiline in the combination therapy of MDR-TB in accordance with the existing guidelines\(^1\). Bedaquiline may be added to a WHO-recommended regimen in adult MDR-TB patients (conditional recommendations/very low quality of evidence) when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed, and/or when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance. Bedaquiline may be indicated when a WHO-recommended regimen is not feasible because of \textit{in vitro} resistance to a drug, known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen, or unavailability of lack of a guaranteed supply of a drug(s).

Bedaquiline can be used for a maximum duration of 6 months and should be used at the suggested dosing (400 mg daily for the first two weeks, followed by 200 mg three times per week for the remaining 22 weeks).

The interim guidance lists five conditions that must be in place if bedaquiline is used to treat adults with MDR-TB:

1. Effective treatment and monitoring: Treatment must be closely monitored for effectiveness and safety, using sound treatment and management protocols approved by relevant national authorities. This includes baseline testing and monitoring for QT prolongation and development of arrhythmia and clinical management and monitoring of comorbidities, particularly cardiac and liver disease.
2. Proper patient inclusion: Special caution is required when bedaquiline is used in people aged 65 and over, and in adults living with HIV. Use in pregnant women and children is not advised.

3. Informed consent: Patients must be fully aware of the potential benefits and harms of the new drug, and give documented informed consent before embarking on treatment.

4. Adherence to WHO recommendations: All principles on which WHO-recommended MDR-TB treatment regimens are based, must be followed, particularly the inclusion of four effective second-line drugs. In line with general principles of TB therapeutics, bedaquiline alone should not be introduced into a regimen in which the companion drugs are failing to show effectiveness.

5. Active pharmacovigilance and management of adverse events: Active pharmacovigilance measures must be in place to ensure early detection and proper management of adverse drug reactions and potential interactions with other drugs. Caution should be exercised when giving bedaquiline together with accompanying drugs that may inhibit liver function.


9.3 Need for special diagnostics, treatment or monitoring facilities and skills

Bedaquiline should only be administered as part of a MDR-TB regimen. It is recommended that bedaquiline is administered by DOT.

The prescribing physician should refer to WHO and/or national TB treatment guidelines for direction on selection and duration of use of companion drugs. Bedaquiline should only be used in combination with at least three drugs to which the patient’s isolate has been shown to be susceptible \textit{in vitro}. If \textit{in vitro} testing results are unavailable, treatment may be initiated with bedaquiline in combination with at least four other drugs to which the patient's isolate is likely to be susceptible.

Throughout treatment with, and following the last intake of, bedaquiline patients should continue to take their companion drugs in accordance with national TB treatment guidelines and local MDR-TB treatment practice.

WHO recommends that active pharmacovigilance measures be put in place to ensure the early detection and timely reporting of adverse events related to the use of bedaquiline. Monitoring of patients for cardiac dysrhythmias or QT prolongation, liver dysfunction, and renal impairment is required.

10. Summary of comparative effectiveness in a variety of clinical settings:

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
To identify peer-reviewed clinical trial data for bedaquiline we utilized the publically available http://www.ncbi.nlm.nih.gov/pubmed website. Using this website we conducted a search using the following search details:

("Bedaquiline" OR "tmc207" AND Clinical Trial)

10.2 Summary of available data

From the results of the search described above, the following publications were considered most relevant to summarizing the available clinical data on bedaquiline effectiveness:


In addition to these publications, we have summarized data from a number of Janssen-prepared documents, including clinical study reports.

10.3 Summary of available estimates of comparative effectiveness

Clinical studies
A Phase 2b, placebo controlled, double blind, randomized trial (C208) was conducted to evaluate the antibacterial activity, safety, and tolerability of bedaquiline in newly diagnosed patients with sputum smear-positive pulmonary MDR-TB including patients with pre-XDR-TB. Patients were randomized to receive treatment with either bedaquiline (n = 79) or placebo (n = 81) for 24 weeks in combination with a preferred 5-drug background regimen of MDR-TB medication consisting of ethionamide (ETH), kanamycin (KAN), pyrazinamide (PZA), ofloxacin (OFL), and cycloserine/terizidone. After the 24-week investigational period, the background regimen was continued to complete 18 to 24 months of total MDR-TB treatment. A final evaluation was conducted at Week 120. Main demographics were as follows: 63.1% of the study population was male, with a median age of 34 years, majority (35% [n = 56]) were Black and 15% (n = 24) patients were HIV positive. Most patients had cavitation in one lung (57.5%); cavitation in both lungs was observed in 16.3% of patients. Of the primary efficacy analysis population, 111 patients had isolates with full
characterization of resistance status. 75.7% (84/111) of patients were infected with an MDR-TB strain and 24.3% (27/111) were infected 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/week for the following 22 weeks. After the double-blind treatment phase patients continued to receive their background MDR-TB treatment until a total treatment duration of 18 to 24 months was achieved, or at least 12 months after the first confirmed negative culture.

The primary outcome parameter was the time to sputum culture conversion (i.e. the interval in days between the first bedaquiline intake and the date of the first of two consecutive negative liquid cultures from sputum collected at least 25 days apart) during treatment with bedaquiline or placebo.

The addition of bedaquiline to a preferred background regimen of MDR-TB treatment resulted in a decreased time to culture conversion and improved culture conversion rates compared to placebo. Median time to culture conversion according to the primary analysis method was 83 days for the bedaquiline group compared to 125 days for the placebo group ($p < 0.0001$; hazard ratio, 95% CI: 2.44 [1.57; 3.80]). The proportion of patients in the modified intent-to-treat (mITT) population with sputum culture conversion after 24 weeks of treatment with bedaquiline or placebo in combination with background regimen (with patients who discontinued considered as non responders), was 52/66 (78.8%) in the bedaquiline group and 38/66 (57.6%) in the placebo group. 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-TB resistant to only rifampin and isoniazid. The rates of culture conversion in patients with MDR-TB resistant to only rifampin and isoniazid were 82.1% (32/39) in the bedaquiline group and 62.2% (28/45) in the placebo group. In addition, in the subgroup of patients infected with a pre-XDR-TB strain, a higher rate of culture conversion was seen in the bedaquiline group [73.3% (11/15)] vs. the placebo group [33.3% (4/12)].

Cure rates according to the WHO definition† were statistically higher in the TMC207 group (38 subjects, 57.6%) than in the placebo group (21 subjects, 31.8%; $p = 0.003$)*

Durability of response seen in the bedaquiline treatment group was supported by the results as shown below. The proportion of responders (with patients who discontinued considered as non responders) at Week 120 was 41/66 (62.1%) in the bedaquiline group and 29/66 (43.9%) in the placebo group.
Table 1: Culture conversion Status

<table>
<thead>
<tr>
<th>Culture Conversion Status, n (%)</th>
<th>mITT population</th>
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<tr>
<td></td>
<td>Bedaquiline/BR</td>
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<tr>
<td></td>
<td>N = 66</td>
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<tr>
<td>Overall responder at Week 24</td>
<td>52 (78.8%)</td>
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<tr>
<td>Overall responder at Week 120</td>
<td>41 (62.1%)</td>
</tr>
<tr>
<td>Overall non-responder* at Week 120</td>
<td>25 (37.9%)</td>
</tr>
<tr>
<td>Failure to convert</td>
<td>8 (12.1%)</td>
</tr>
<tr>
<td>Relapse†</td>
<td>6 (9.1%)</td>
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<tr>
<td>Discontinued but converted</td>
<td>11 (16.7%)</td>
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mITT = modified intent-to-treat; BR = background regimen

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

† Relapse was defined in the trial as having a positive sputum culture after or during treatment following prior sputum culture conversion.

A Phase 2b, open label trial (C209) was conducted to evaluate the safety, tolerability, and efficacy of bedaquiline as part of an individualized MDR-TB treatment regimen in 233 patients with sputum smear positive (within 6 months prior to screening) pulmonary MDR-TB. Main demographics were as follows: 64% of the study population was male, median age 32, majority were Asian (39%) or Black (32%) and 11 patients (5%) were HIV positive. About half of the patients (51.9%) had cavitation in only one lung; 11.6% had cavitation in both lungs and 36.5% had no cavitation. Of the primary efficacy analysis population, 174 patients had isolates with full characterization of resistance status. 53.4% (93/174) of patients were infected with an MDR strain, 25.3% (44/174) of patients were infected with a pre-XDR strain, and 21.3% (37/174) of patients were infected with an XDR strain.
Patients received bedaquiline for 24 weeks in combination with an individualized background regimen of antibacterial drugs: fluoroquinolones [89.3%; mainly ofloxacin: (52.4%) and levofloxacin: (30.5%)], pyrazinamide (76.0%), aminoglycosides (72.1%; mainly kanamycin: 50.2%), and ethambutol (51.9%). Other baseline background regimen drugs taken by > 40% of patients were PAS C (46.4%) and ethionamide (42.1%). Bedaquiline was administered as 400 mg once daily for the first 2 weeks and as 200 mg 3 times/week for the following 22 weeks. Upon completion of the 24 week treatment with bedaquiline, all patients continued to receive their background regimen in accordance with national TB program (NTP) treatment guidelines. A final evaluation was conducted at Week 120.

The primary efficacy endpoint was the time to sputum culture conversion during treatment with bedaquiline (with patients who discontinued considered as non-responders). Median time to sputum culture conversion excluding patients with drug–sensitive TB (DS-TB) and those that did not have a positive sputum culture at screening and/or baseline (mITT; 205 patients), was 57 days. At Week 24, 163 of 205 (79.5%) patients responded to bedaquiline treatment as determined by sputum culture conversion rates. Conversion rates at Week 24 were highest (87.1%; 81/93) in patients with MDR-TB resistant to only rifampin and isoniazid, 77.3% (34/44) in pre-XDR-TB patients and lowest (54.1%; 20/37) in XDR-TB patients.

According to the WHO definition of cure†, 125 (61.0%) subjects were considered cured at the end of the study.*

At Week 120, 148 of 205 (72.2%) patients responded to bedaquiline treatment as determined by sputum culture conversion rates. Conversion rates at Week 120 were highest (73.1%; 68/93) in patients with MDR-TB resistant to only rifampin and isoniazid, 70.5% (31/44) in pre-XDR-TB patients and lowest (62.2%; 23/37) in XDR-TB patients.

At both Week 24 and Week 120, responder rates were higher for patients on 3 or more active drugs (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.

Although there were differences in background regimens used across trials, safety results were generally similar between trials C208 and C209.

Clinical study evaluating the QTc interval

The effect of a single supratherapeutic bedaquiline 800 mg dose on QTc interval was evaluated in a double-blind, randomized, placebo-, and positive-controlled (moxifloxacin
400 mg) parallel group QT study in 44 healthy subjects. The placebo-adjusted maximum mean increase in QTcF was 5.2 ms, 90% confidence interval [CI]: [1.5, 8.9]). The upper limit of the 90% CI was below the threshold of 10 ms indicating that this thorough QT study did not reveal a clinically significant effect of bedaquiline on the QT interval. Trial (assay) sensitivity was demonstrated with moxifloxacin.

However, an increase in QTcF when using bedaquiline was demonstrated in the Phase 2 studies.

*WHO definition of cure: An MDR-TB subject who completed the study and has been consistently culture-negative (with at least five consecutive negative cultures from samples collected at least 30 days apart) for at least the final 12 months of the study. If only one positive culture is reported during that time, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

11. Summary of comparative evidence on safety:

11.1 Estimate of total patient exposure to date

**ESTIMATED EXPOSURE**

**Cumulative Subject Exposure in Clinical Trials**

Overall, 400 subjects without TB, of which 376 were healthy subjects, 8 subjects were hepatic impaired and 16 subjects were human immunodeficiency virus (HIV) infected and 516 subjects with TB have been enrolled in the Company-sponsored bedaquiline clinical programme. Up to 5 September 2014, the compassionate use programmes have enrolled 518 subjects and the early access trial has enrolled 57 subjects.

A total of 681 subjects have received bedaquiline in the Company-sponsored clinical trials. Of these, 301 subjects were exposed to bedaquiline in the Phase 1 programme and 380 subjects were exposed to bedaquiline in the Phase 2 programme. In non-company sponsored clinical trials, 267 subjects (70 subjects in the National Institute of Health (NIH) sponsored trials and 197 subjects in the TB Alliance sponsored trials) were exposed to bedaquiline.

**Cumulative and Interval Patient Exposure From Marketing Experience**

Based on the distribution of 2,857.6 g of finished product distributed (from launch to August 2014), the estimated exposure to bedaquiline is 152 completed treatment courses. Company JSC “Pharmstandard-Ufa Vitamin Plant”, the marketing authorization holder for SIRTURO® (Bedaquiline) on the territory of the Russian Federation, provided the MAH with the following information on drug usage:

- Up to 5 September 2014, 3,083.2 g of finished product was distributed.
- Up to 5 September 2014, the estimated exposure on the territory of the Russian Federation is 164 treatment courses.

Based on the total distribution of 5,940.8 g of finished product distributed, the cumulative estimated postmarketing exposure to bedaquiline in all territories is 316 completed treatment courses.
11.2 Description of adverse effects/reactions

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of bedaquiline based on the comprehensive assessment of the available adverse event information. A causal relationship with bedaquiline cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse drug reactions (ADRs) for bedaquiline were identified from pooled Phase 2b clinical trial data (both controlled and uncontrolled) containing 335 patients who received bedaquiline in combination with a background regimen of TB drugs. The basis of assessment of causality between the ADRs and bedaquiline was not restricted to these trials but also on review of the pooled Phase 1 and Phase 2a safety data.

The most frequent ADRs (> 10.0% of patients) during treatment with bedaquiline in the controlled trials were nausea, arthralgia, headache, vomiting and dizziness.

Adverse drug reactions to bedaquiline are presented in Table 2. Adverse drug reactions are listed by system organ class (SOC) and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

<table>
<thead>
<tr>
<th>Table 2: All Adverse Drug Reactions from Controlled Trials During Treatment with bedaquiline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Drug Reactions</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
</tr>
<tr>
<td>ECG QT prolonged</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
</tbody>
</table>
Nausea | Very Common | 36 (35.3) | 27 (25.7)
--- | --- | --- | ---
Vomiting | Very Common | 21 (20.6) | 24 (22.9)
Diarrhea | Common | 6 (5.9) | 12 (11.4)

**Hepatobiliary disorders**

Transaminases Increased* | Common | 7 (6.9) | 1 (1.0)

**Musculoskeletal and connective tissue disorders**

Arthralgia | Very Common | 30 (29.4) | 21 (20.0)

Myalgia | Common | 6 (5.9) | 7 (6.7)

* Terms represented by ‘transaminases increased’ included AST increased, ALT increased, hepatic enzyme increased, hepatic function abnormal, and transaminases increased.

No additional ADRs were identified from the uncontrolled study C209 (N = 233) nor from the Phase 1 and 2a studies.

**Deaths:**

In the C208 trial, there were more deaths reported in the bedaquiline treatment group. In the bedaquiline treatment group, the most common cause of death as reported by the investigator was TB (5 patients). All of the deaths due to TB occurred in patients whose sputum culture status at last visit was ‘not converted’. The causes of death in the remaining bedaquiline patients varied. In addition, the imbalance in deaths is unexplained; no discernible pattern between death and sputum conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, and severity of disease was observed.

During the trial, there was no evidence of antecedent significant QTcF prolongation or clinically significant dysrhythmia in any of the patients that died. See Table 3 for a summary of deaths in the C208 trial.

<table>
<thead>
<tr>
<th>Table 3: Summary of Deaths During the C208 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bedaquiline/BR Group</strong></td>
</tr>
<tr>
<td><strong>Cause of Death</strong></td>
</tr>
</tbody>
</table>

<p>| | | | | |
|  |  |  |  |  |</p>
<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Duration of Exposure* (days)</th>
<th>Days Since Last Study Drug Intake</th>
<th>Sputum Culture Status at Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoptysis</td>
<td>168</td>
<td>105</td>
<td>not converted</td>
</tr>
<tr>
<td>Tuberculosis-related illness</td>
<td>165</td>
<td>709</td>
<td>not converted</td>
</tr>
<tr>
<td>Tuberculosis-related illness</td>
<td>128</td>
<td>1048</td>
<td>converted</td>
</tr>
</tbody>
</table>

BR = background regimen of multidrug resistant tuberculosis medication consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone

* the duration of exposure refers to blinded study drug administration

† died after the end of the investigational period

§ died after prematurely discontinuing from the trial

# died during the investigational period when bedaquiline was administered
In the open-label C209 trial, 6.9% (16/233) patients died. The most common cause of death as reported by the investigator was TB (9 patients). All but one patients who died of TB had not converted or had relapsed. The causes of death in the remaining patients varied.

**Cardiovascular safety:**

In the controlled Phase 2b study (C208), mean increases in QTcF were observed 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 in QTcF during the 24 weeks of bedaquiline treatment was 15.7 ms (at Week 18). After the end of bedaquiline treatment (i.e. after Week 24), QTcF increases in the bedaquiline group gradually became less pronounced. The largest mean increase in QTcF in the placebo group during the first 24 weeks was 6.2 ms (at Week 18).

11.3 **Identification of variation in safety due to health systems and patient factors**

Patient populations for which limited or no data of bedaquiline treatment are currently available, and therefore no safety conclusions can be drawn, include subjects with cardiovascular risk factors, severe hepatic impairment, severe renal impairment, elderly (aged ≥65 years), pediatrics (aged <18 years), pregnant or breastfeeding women, subjects with different manifestations of TB disease, HIV-coinfected subjects receiving concomitant ARV treatment and subjects of different racial and/or ethnic origin.

Other factors related to health systems that could impact patient safety would be the inability to conduct adequate monitoring, i.e. regular ECGs, monitoring of liver enzymes, monitoring of electrolytes.

11.4 **Summary of comparative safety against comparators**

Please refer to section 11.2

12. **Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:**

12.1 **Range of costs of the proposed medicine**

A tiered pricing strategy for sustainable and affordable access to bedaquiline is being implemented globally. Medicine costs will be lowest in the low and lower middle income countries that will be able to access the drug via the Stop TB Partnership’s Global Drug Facility (GDF) and highest in advanced economies. All medicine costs will be at below evidence-based value. This comprehensive Access & Affordability approach is in view of the unique public health considerations of MDR-TB. It is Janssen’s policy to only communicate prices after regulatory approval and discussions with local health authorities. The following prices are publicly available.
<table>
<thead>
<tr>
<th>Country</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Income Countries</strong></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>EUR 22,585</td>
</tr>
<tr>
<td>Belgium</td>
<td>EUR 23,350</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>EUR 22,191.60</td>
</tr>
<tr>
<td>Denmark</td>
<td>EUR 31,388.81</td>
</tr>
<tr>
<td>Finland</td>
<td>EUR 28,105.40</td>
</tr>
<tr>
<td>France</td>
<td>EUR 23,428.12</td>
</tr>
<tr>
<td>Germany</td>
<td>EUR 32,998.15</td>
</tr>
<tr>
<td>Italy</td>
<td>EUR 22,228.81</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>EUR 23,350</td>
</tr>
<tr>
<td>Norway</td>
<td>EUR 22,664</td>
</tr>
<tr>
<td>Romania</td>
<td>USD 15,375</td>
</tr>
<tr>
<td>Russia</td>
<td>USD 2,800</td>
</tr>
<tr>
<td>Slovakia</td>
<td>EUR 22,191.60</td>
</tr>
<tr>
<td>Slovenia</td>
<td>EUR 24,768.13</td>
</tr>
<tr>
<td>Sweden</td>
<td>EUR 23,065.43</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>EUR 23,350</td>
</tr>
<tr>
<td>The United Kingdom</td>
<td>GBP 18,700</td>
</tr>
<tr>
<td>United States of America</td>
<td>USD 30,000</td>
</tr>
<tr>
<td><strong>Low &amp; Middle Income Countries</strong></td>
<td></td>
</tr>
<tr>
<td>Albania, Algeria, Azerbaijan, Belarus, Bosnia &amp; Herzegovina, Brazil, Colombia, Ecuador, Kazakhstan, Serbia, Lebanon, Libya, Palau, Peru, Tunisia, TFYR Macedonia, Turkmenistan</td>
<td>USD 3,000</td>
</tr>
<tr>
<td>Thailand</td>
<td>USD 1,424.92</td>
</tr>
</tbody>
</table>
Bedaquiline can be made available in the countries listed above. Marketing Authorization has been obtained for bedaquiline in the USA, Russia Federation, European Union, South Korea, South Africa, and the Philippines.

For most patients with MDR-TB, an intensive phase of 8 months and total treatment duration of 20 months is suggested in WHO guidelines; the duration may be modified according to the patient’s response to therapy. Bedaquiline is indicated in adults (≥18 years) as part of combination therapy of pulmonary TB due to MDR-TB. The total duration of treatment with bedaquiline is 24 weeks. The WHO issued interim policy guidance on the use of bedaquiline in the treatment of MDR-TB, indicating that bedaquiline may be added to a WHO-recommended regimen for the treatment of MDR-TB provided the following five conditions are met:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective treatment and monitoring</td>
<td>Treatment must be closely monitored for effectiveness and safety, using sound treatment and management protocols approved by relevant national authorities</td>
</tr>
<tr>
<td>Proper patient inclusion</td>
<td>Special caution is required when Sirturo® is used in people aged 65 and over, and in adults living with HIV. Use in pregnant women and children is not advised</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Patients must be fully aware of the potential benefits and harms of the new drug, and give documented informed consent before embarking on treatment</td>
</tr>
<tr>
<td>Adherence to WHO recommendations</td>
<td>All principles on which WHO-recommended MDR-TB treatment regimens are based, must be followed, particularly the inclusion of four effective second-line drugs. In line with general principles of TB therapeutics, Sirturo® alone should not be introduced into a regimen in which the companion drugs are failing to show effectiveness</td>
</tr>
<tr>
<td>Active pharmacovigilance and management of AEs</td>
<td>Active pharmacovigilance measures must be in place to ensure early detection and proper management of adverse drug reactions and potential interactions with other drugs</td>
</tr>
</tbody>
</table>

WHO recently issued a “Policy Implementation Package for New TB Drug Introduction”, to support countries in preparing for introduction of new TB drugs and/or regimens, based on WHO policy guidance, in order to better serve patients and communities in need. The package focuses on six core elements that need to be in place when introducing a new TB drug or regimen, including:

1. Minimum requirements for country preparedness and planning.
2. National Implementation plan for introduction of new TB drugs and/or regimens.
3. Monitoring and evaluation of new drugs and regimens, including pharmacovigilance and drug resistance surveillance.
4. Private sector engagement.
5. Systems approach for ensuring uninterrupted supply of quality-assured drugs.
6. Operational research

This package is being rolled out in several countries designated as “early adopters” of bedaquiline to develop national introduction plans; recent experiences from South Africa, Viet Nam, Philippines, Indonesia, and Kazakhstan in preparing for introduction of bedaquiline into their treatment programmes was recently shared at an international conference\(^1\).


\(^2\) WHO (2013). The use of bedaquiline in the treatment of multi-drug resistant tuberculosis


\(^4\) WHO & BMGF (2014). Programmatic Implementation of New Drugs for the Treatment of MDR-TB: Progress from the Field

12.2 Comparative cost-effectiveness (presented as range of cost per routine outcome) (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

Three studies are available that document the costs and cost-effectiveness of adding bedaquiline to an MDR-TB regimen; one, commissioned by WHO as part of the evidence-based for the development of the Interim Policy Guidance on Bedaquiline focused on low and middle income countries\(^1\) (Russia, Estonia, Philippines, Peru, Nepal, and China), and two others focused on high-income countries (the UK\(^2\) and Germany\(^3\)). The study in low and middle income settings found that bedaquiline is highly likely to be cost-effective in most environments, for a wide range of assumptions about the translation of trial results to current practice.

Table 4: Cost & Cost-Effectiveness of adding Bedaquiline to MDR-TB treatment regimens in low and middle income countries\(^1\)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost to treat MDR-TB without bedaquiline (USD)</th>
<th>Incremental cost of adding bedaquiline to the MDR-TB treatment regimen (USD)</th>
<th>Incremental cost per DALY gained (point estimate &amp; range) (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal(^a)</td>
<td>$2,577</td>
<td>$404</td>
<td>$824</td>
</tr>
<tr>
<td>Peru(^a)</td>
<td>$3,212</td>
<td>$422</td>
<td>$849</td>
</tr>
<tr>
<td>The Philippines(^a)</td>
<td>$4,023</td>
<td>$595</td>
<td>$977</td>
</tr>
<tr>
<td>China(^b)</td>
<td>$9,694</td>
<td>$1,535</td>
<td>$2,788</td>
</tr>
<tr>
<td>Estonia(^c)</td>
<td>$12,549</td>
<td>$775</td>
<td>$2,920</td>
</tr>
<tr>
<td>Russia(^d)</td>
<td>$18,291</td>
<td>$898</td>
<td>$2,719</td>
</tr>
</tbody>
</table>

\(^a\) Assumed price of bedaquiline at US $900 per patient

\(^b\) Assumed price of bedaquiline at US $3,000 per patient
In Germany, adding bedaquiline to the background regimen for the treatment of MDR-TB resulted in an additional cost per patient of €3518 (based on a price of €33,000 per treatment course of bedaquiline), and the incremental cost-effectiveness ratio was €3,369 per QALY gained; a probabilistic sensitivity analysis showed that the likelihood of adding bedaquiline to MDR-TB treatment regimens as 82%-95% likely to be cost-effective.

In the UK, bedaquiline is likely to be cost-saving; the incremental cost per patient of adding bedaquiline to MDR-TB treatment regimens is estimated at -£11,434 (based on an assumed price of -£18,800 per treatment course of bedaquiline). Because bedaquiline leads to faster (and higher rates of) culture conversion, and UK patients are typically hospitalized until culture conversion, substantial savings can be realized from consequent reductions in duration of hospitalizations. 1.14 QALYS are gained per patient treated with bedaquiline, and there is a reduction in DALYS lost from 13.78 to 9.21 per patient treated. Regardless of whether one looks at cost per QALY or cost per DALY, adding bedaquiline to the treatment of MDR-TB dominates, at -£10,008.75 per QALY gained or -£2,504.95 per DALY averted. Probabilistic sensitivity analyses indicated the probability of bedaquiline being cost-effective was between 96%-99%.


13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well).

See Registration status spreadsheet attached


There are no compendial monographs established at this time.

15. Proposed (new/adapted) text for the WHO model formulary

Bedaquiline 100 mg tablet

Bedaquiline is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.