WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

Bedaquiline 100mg tablet
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE  Adverse events
ALP  Alkaline phosphatase
ALT  Alanine aminotransferase
AST  Aspartate aminotransferase
ATP  Adenosine 5’-triphosphate
AUC  Area under the plasma concentration versus time curve
CDC  Center of Disease Control (US)
CFU  Colony forming unit
CFZ  Clofazimine
Cmax  Maximum plasma concentration
DOT  Directly observed therapy
DS  Drug-susceptible
ECG  Electrocardiogram
EMA  European Medicines Agency
FDA  Food and Drug Administration
GGT  Gamma-glutamyltransferase
HIV  Human immunodeficiency virus
INN  International non-proprietary name
ITT  Intent-to-treat
MDR-TB  Multidrug-resistant tuberculosis including pre-XDR- and XDR-TB (see “definitions of terms”)
M. tuberculosis  Mycobacterium tuberculosis
QALY  Quality Adjusted Life Year
SAE  Serious adverse event
SOC  Standard of care
TB  Tuberculosis
WHO  World Health Organization
XDR-TB  Extensively drug-resistant tuberculosis

1. Summary statement of the proposal for inclusion, change or deletion:

Inclusion of the tablet formulation of bedaquiline 100 mg is proposed for treatment of pulmonary multidrug-resistant tuberculosis (MDR-TB) among adults (≥18 years) as part of combination therapy.

The principal reasons for requesting this inclusion are as follows:

1. Appropriate treatment of MDR-TB remains a major challenge globally, in particular in high-TB burden countries.
2. The target treatment success rate for patients with MDR-TB remains low. Only 30 of 107 countries that reported treatment outcomes reached the target treatment success rate of 75% or higher1.

3. Levels of MDR-TB remain high in areas of the world, in particular countries in Eastern Europe and central Asia. In several of these countries, 9–32% of new cases have MDR-TB and more than 50% of previously treated cases have MDR-TB1.

4. 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.

5. The distinct target (ATP synthase inhibition) of bedaquiline ensures the absence of cross-resistance with existing anti-TB drugs.

6. Treatment outcomes of MDR-TB will be improved with the addition of bedaquiline to current treatment regimens.

7. 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.

1WHO. Global Tuberculosis Report 2012.

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

   Christian Lienhardt, Stop TB Department, WHO

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

   Janssen Research & Development, LLC
   Turnhoutseweg 30, Beerse, 2340 Belgium
   Contact: Mercè Caturla, Global Regulatory Affairs

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

   Bedaquiline

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

   Adult: Uncoated, immediate-release oral tablet (100 mg).
   Pediatric: There is currently no pediatric formulation.

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

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

   Trade name: Sirturo™

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group:
Since bedaquiline is indicated for the treatment of MDR-TB, inclusion within the Complementary List of 6.2.4 Antituberculosis medicines 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’ is requested.

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

Among the world’s 12 million prevalent cases of TB globally in 2011, there were an estimated 630 000 cases of MDR-TB (range, 460 000–790 000)\(^1\).

From a geographic perspective, the greatest burden of TB is in Asia and Africa with almost 60% of the world’s TB cases in India, China, Russia and South Africa combined. The majority (almost 80%) of TB cases among individuals with HIV are in Africa. The highest proportion of TB patients with MDR-TB is in Eastern Europe and central Asia. Approximately 9–32% of new cases and more than 50% of previously treated cases have MDR-TB in several of these countries. Globally, 3.7% (2.1–5.2%) of new cases and 20% (13–26%) of previously treated cases are estimated to have MDR-TB\(^1\). TB disproportionately affects low- and middle-income countries.

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\(^2\). For patients with MDR-TB on treatment, treatment success remains low with cure rates typically ranging from 50% to 70%\(^3\). Only 30 of 107 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\(^5\).

Globally, extensively drug-resistant TB (XDR-TB) has been identified in 84 countries. The average proportion of MDR-TB cases with XDR-TB is 9.0%\(^1\).

\(^1\)WHO. Global Tuberculosis Report 2012.

8.2 Assessment of current use
Statistics on the number of persons on bedaquiline have not yet been collected; only clinical trial data are available (see Sections 10 and 11). Cumulative exposure will be estimated for pharmacovigilance.

8.3 Target population
Newly diagnosed patients (adults ≥18 years) with pulmonary disease caused by MDR-TB, defined as isolates with in vitro resistance to at least isoniazid and rifampicin.

9. Treatment details:
9.1 Dosage regimen, duration
Bedaquiline is indicated in adults (≥18 years) as part of combination therapy of pulmonary TB due to MDR-TB.

Adults (≥18 years):
Bedaquiline should only be administered as part of a MDR-TB regimen. It is recommended that bedaquiline is administered by directly observed therapy (DOT).

The recommended dosage of bedaquiline for MDR-TB is:
- Weeks 1 and 2: 400 mg (four tablets of 100 mg) once daily
- Weeks 3 to 24: 200 mg (two tablets of 100 mg) three 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.

Pediatric population:
The safety and efficacy of bedaquiline in children and adolescents <18 years of age have not been established.

Elderly population:
There are limited data on the use of bedaquiline in elderly patients.

Hepatic impairment:
The pharmacokinetics of bedaquiline was assessed after single dose administration to subjects with moderate hepatic impairment (Child Pugh B) (see section 5.2). 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.

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.

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 rifampicin. For most patients diagnosed with MDR-TB, WHO recommends treatment for 20 months with a regimen that includes second-line anti-TB drugs. WHO Guidelines¹ 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 the new drug application submitted by Janssen to the US Food and Drug Administration (FDA), bedaquiline is proposed for the treatment of pulmonary TB due to MDR-TB in adults (≥18 years), as part of combination therapy. It is recommended that bedaquiline be administered by DOT. The prescribing physician should refer to the prescribing information of bedaquiline and to national TB treatment guidelines for direction on selection and duration of use of companion drugs. To minimize the risk of development of resistance to the drug, bedaquiline should only be used in combination with at least three drugs to which the patient’s isolate has been shown to be susceptible in vitro. If 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, based on local TB drug resistance data and the patient’s previous TB treatment exposure. The total duration of treatment with bedaquiline is 24 weeks. 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.

In the Summary of Product Characteristics submitted by Janssen to the European Medicines Agency (EMA), 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 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 in vitro. If 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.

1WHO. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update.

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 in vitro. If 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.

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"[Supplementary Concept] OR "Bedaquiline"[All Fields] OR "tmc207"[All Fields]) AND Clinical Trial[ptyp]

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

Initial studies assessing the pharmacokinetics of bedaquiline in healthy volunteers:
According to a new drug application for bedaquiline prepared by Janssen and submitted to the FDA, three Phase II trials have been conducted or are ongoing. Prior to these trials, the pharmacokinetics of bedaquiline were evaluated in healthy male volunteers in a double-blind, randomized, placebo-controlled clinical study. Six cohorts of nine volunteers were enrolled. Volunteers within each cohort were randomized 2:1 to receive either a single oral dose of bedaquiline or placebo. Six escalating doses of 10, 30, 100, 300, 450 and 700 mg bedaquiline were administered to the cohorts.

The mean plasma concentration–time profiles showed that bedaquiline was well absorbed after a single oral dose and that $C_{\text{max}}$ was reached 5 hours after dosing. After $C_{\text{max}}$ was reached, bedaquiline concentration declined triexponentially with time. Additionally, $C_{\text{max}}$ and AUC increased proportionally with the administered dose and there was no dose-dependent change in the terminal half-life.

A similar design to the single-dose study was utilized in a multiple-dose study. Three cohorts of 9 healthy male volunteers were recruited. Within each cohort, volunteers were randomized 2:1 to receive a daily oral dose of bedaquiline or placebo for 14 days. Three escalating doses of 50, 150 and 400 mg bedaquiline were administered to the cohorts. In this study, an increase by a factor of ~2 in the AUC$_{0-24}$ between day 1 and day 14 was observed, suggesting an “effective half-life” of 24 hours.

Proof-of-principle studies in treatment-naïve patients:
Trial C202 was a proof-of-principle, open-label, randomized phase IIa trial in treatment naïve patients with sputum smear-positive pulmonary DS-TB. Although HIV-positive patients were allowed, those receiving antiretroviral therapy were excluded. Patients received either one of three different doses of bedaquiline (25, 100 and 400 mg), 600 mg of rifampin, or 300 mg of isoniazid, once-daily. The efficacy of treatments was assessed by the change in CFU count from baseline over a 7-day period.
Seventy-five patients were randomized, of which 67 (89%) completed the study. Demographic and baseline measurements were similar between the five treatment groups. Patients were 60% male and 57% black. The median age of patients was 34 years (range 18–61) and 56% were active smokers. Thirty-one percent of patients were HIV-positive with a median CD4 T-cell count of 510 cells/mL.

Patients were hospitalized during the study period and 16-hour overnight sputum samples were collected daily. Table 10.1 shows the mean changes in CFU counts from baseline. During the 7 days of treatment, the reduction in CFU was found to be greater in the rifampin and isoniazid groups compared to the bedaquiline groups. Mean changes in sputum CFU counts were -0.01, -0.04 and -0.11 log_{10} CFU/day for the bedaquiline 25, 100 and 400 mg groups, respectively. Corresponding values for the control groups were -0.24 log_{10} CFU/day for the rifampin group and -0.27 log_{10} CFU/day for the isoniazid group.

The largest decreases in CFU counts induced by rifampin or isoniazid were observed during the first 3 days of treatment. The bactericidal activity of bedaquiline was observed later in the treatment period, resulting in smaller overall decreases in CFU counts. However, over days 4 to 7, 400 mg bedaquiline showed comparable decreases in CFU counts to rifampin and isoniazid (-0.55, -0.53 and -0.56 log_{10} CFU, respectively).

In a prospective, early bactericidal activity study, treatment-naïve, DS patients were randomized to receive bedaquiline, bedaquiline-pyrazinamide, PA-824-pyrazinamide, bedaquiline-PA-824, PA-824-moxifloxacin-pyrazinamide, or unmasked standard anti-TB treatment as positive control. The primary efficacy assessment was made by measuring the daily fall in CFU/mL of sputum in daily overnight sputum collections. The mean 14-day early bactericidal activity of PA-824-moxifloxacin-pyrazinamide was significantly higher than that of bedaquiline (0.233 [SD 0.128] vs. 0.061 [0.068]).

Studies assessing efficacy of bedaquiline in patients with MDR-TB:
Trial C208 was a Phase IIb, randomized, placebo-controlled trial consisting of an 8-week exploratory stage followed by a separate 24-week proof-of-efficacy stage. In the first stage, 47 patients with newly diagnosed MDR-TB were randomly assigned to receive either...
bedaquiline (400 mg once-daily for 2 weeks, followed by 200 mg three times a week for 6 weeks) or placebo, in combination with a standard five-drug, second-line anti-TB regimen. The primary efficacy end point was time to culture conversion in liquid broth during the 8-week treatment period.

Of the 47 patients randomized to bedaquiline or placebo, 41 patients completed the treatment period (20/23 in the bedaquiline group and 21/24 in the placebo group). There were no significant differences in demographic of baseline measurements between the two treatment arms. Patients were 74% male and 55% black. The median age of patients was 33 years (range 18–57). The majority of patients were HIV-negative (87%)\(^6\).

The addition of bedaquiline to the standard second-line drug regimen resulted in earlier conversion to a negative sputum culture, compared with a standard five-drug, second-line anti-TB regimen. The rates of conversion to a negative culture were 48% in the bedaquiline treatment arm and 9% in the placebo group (Figure 10.1a). Additionally, over the course of the treatment period, reductions from baseline in the median log\(_{10}\) CFU count in the bedaquiline group were greater at all time points than reductions in the placebo group (Figure 10.1b)\(^6\).

Blood samples were taken before dosing at weekly intervals during the bedaquiline treatment phase to determine plasma concentrations of bedaquiline. Furthermore, 24-hour and 48-hour blood sampling was conducted at week 2 and week 8, respectively, for full pharmacokinetic profiling. Steady-state plasma concentrations of bedaquiline were 1770±701 ng/mL and 902±535 ng/mL at week 2 and week 8, respectively. The majority of patients achieved steady-state plasma bedaquiline concentrations above the target 600 ng/mL throughout the bedaquiline treatment phase\(^6\).

Figure 10.1a and 10.1b:

Stage 2 of the C208 trial consisted of a 24-week investigational treatment period and a 96-week follow-up period\(^7\). In Stage 2, 160 patients with MDR-TB were randomized and assigned to receive either bedaquiline (400 mg once-daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) or placebo, in combination with a standard five-drug, second-line anti-TB regimen. The primary efficacy end point was time to culture conversion using Week 24 data. Patients participating in Stage 1 of the C208 trial were not allowed to enter Stage 2.
Of the ITT population, 79 patients received bedaquiline and 81 patients received placebo. Patients were 63% male and 35% black. The median age of patients was 34 years (range 18–63) and the majority of patients were HIV-negative (85%)⁷.

The primary efficacy results from Stage 2 of the C208 trial demonstrate that the addition of bedaquiline to second-line anti-MDR-TB treatment for 24 weeks resulted in significantly shorter time to culture conversion and a significantly higher proportion of culture conversion at 24 weeks. The proportion of patients with culture conversion at Week 24 [missing = failure] was 79% in the bedaquiline group and 58% in the placebo group. The difference in proportion of responders was statistically significant (p = 0.008) based on a logistic regression model with only treatment as covariate.

Importantly, the significantly improved response appears durable, with a lower chance of relapse. Sixty-two percent of patients receiving bedaquiline showed sustained culture conversion at the 96-week follow-up time point versus 44% of the placebo group⁷.

Further, inclusion of bedaquiline treatment in the regimen also markedly decreased the risk of acquiring resistance to other background drugs. In both stages of the C208 trial, an imbalance in resistance amplification was observed with fewer patients developing a pre-XDR- or XDR-TB profile in the bedaquiline group versus placebo group (one vs. four in Stage 1; zero vs. seven in Stage 2 of the C208 trial). Furthermore, in Stage 2, when responders were analyzed based on the extent of their resistance to *M. tuberculosis* it was observed that the bedaquiline group had a better cure rate among patients with MDR-TB (69% vs. 44%), and also patients with pre-XDR-TB (60% vs. 42%)⁷.

Final population pharmacokinetic analysis showed that bedaquiline displayed a multi-phasic distribution and elimination profile with a long terminal elimination half-life of approximately 5.5 months, reflecting the slow release of the compound from peripheral tissue compartments¹.

Time to culture conversion during the 24-week treatment period with bedaquiline was also the primary efficacy outcome parameter for trial C209¹. Trial C209 differs from C208 in that patients were included who were either newly or non-newly diagnosed with MDR-TB, whereas in C208 previous use of second-line drugs was an exclusion criterion. Efficacy results in C209 were generally consistent with those of Stage 2 of the C208 trial.

In the C209 trial, a shorter median time to culture conversion was observed following treatment with bedaquiline for 24 weeks in conjunction with an individually optimized background regimen of anti-TB drugs, compared to the bedaquiline arm in C208 Stage 2. This likely reflects that the majority of C209 trial patients in the ITT population (86%) were receiving anti-TB treatment during the screening phase of the trial¹. The median time to culture conversion in C209 based on the extent of patients’ resistance to *M. tuberculosis* is shown in Figure 10.2.
References

1 Anti-Infective Drugs Advisory Committee Meeting Briefing Document (bedaquiline), 28 November 2012.


7 Clinical study report, 13 November 2012. A Phase II, placebo-controlled, double-blind, randomized trial to evaluate the antibacterial activity, safety, and tolerability of bedaquiline in subjects with sputum smear-positive pulmonary infection with multi-drug resistant Mycobacterium tuberculosis (MDR-TB).

11. Summary of comparative evidence on safety:

11.1 Estimate of total patient exposure to date

A total of 265 patients were exposed to bedaquiline during 11 Phase I single- or multiple-dose studies and 335 patients were exposed to bedaquiline in the Phase II clinical trials (C208 Stage I and II, and C209) with exposure ranging from 1.1–29.1 weeks (median 25 weeks), in the context of company-sponsored trials (clinical supply). Seventy-eight patients have been exposed to bedaquiline across three early access programs that have included
patients who have pulmonary infection due to pre-XDR- or XDR-TB strains and, therefore, have limited-to-no treatment options.

Data for DS-TB patients entering trials sponsored by the Global Alliance for TB Drug Development have not been directly included herein. However, no additional safety indicators have been identified during the trials to date (three completed Phase I trials and two completed Phase II trials, a third Phase II trial is currently recruiting patients). Five SAEs of lymphocytopenia were reported in a drug-drug interaction study with rifabutin, for which lymphopenia is a known adverse drug reaction.1

11.2 Description of adverse effects/reactions

The most frequently reported (in 2% or more patients) adverse events considered at least possibly related to bedaquiline by the investigator in the Phase II studies were: arthralgia, dizziness, headache, hyperuricemia, insomnia, myalgia, nausea, prolonged ECG QT interval, pruritus, and vomiting.

Adverse events considered at least possibly related to bedaquiline by the investigator and reported in less than 2% of patients were: acute pancreatitis, allergic dermatitis, anemia, anorexia, anxiety, asthenia, atrioventricular block, blurred vision, breast mass, breast pain, burning sensation, chest discomfort and pain, chronic obstructive pulmonary disease, conduction disorder, conjunctivitis, constipation, deafness (including unilateral and bilateral), diarrhea, dyspepsia, eye pruritus, gastritis, gynecomastia, hypersensitivity, hypokalemia, muscle spasms, pain, pain in extremity, paraesthesia, peripheral neuropathy, photophobia, rash (generalized, popular and maculo-papular), right bundle branch block, tinnitus, upper abdominal pain, and vertigo.

Increases in the following laboratory parameters were reported as adverse events and considered to be at least possibly related to bedaquiline by the investigator (reported in less than 2% of patients): ALT, ALP, AST, amylase, blood gastrin, creatine phosphokinase, creatine phosphokinase MB, creatinine, hepatic enzymes, lipase, transaminases and uric acid.

Grade 3 or 4 adverse events reported by more than one patient, regardless of causality, during the overall treatment phase of the Phase II studies include: arthralgia, bilateral deafness, dyspnea, hemoptysis, hepatitis, hyperuricemia, leukocytosis, pneumonia, pneumothorax and tuberculosis. The following increases in laboratory parameters were also recorded as grade 3 or 4 adverse events: ALT, AST, GGT, hepatic enzyme, prolonged ECG QT, transaminases and uric acid.

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 patients with cardiovascular risk factors, severe hepatic insufficiency, severe renal insufficiency, elderly (aged ≥65 years), pediatrics (aged <18 years), nursing mothers and during pregnancy.
11.4 Summary of comparative safety against comparators

Bedaquiline has been administered in addition to the standard five-drug, second-line anti-TB regimen. Addition of bedaquiline to the regimen did not result in an increase in adverse events. In the Phase II study, C208 Stage II, the safety of bedaquiline was compared with that of placebo, both combined with the background regimen. Table 11.1 presents a summary of the overall safety profile, which is similar between the two treatment regimens.

Discontinuations as a result of adverse events were similar in the two arms (three patients in the bedaquiline arm vs. two patients in the placebo arm). Further, addition of bedaquiline did not result in increase in adverse events at least possibly related to treatment (70% of patients in the bedaquiline arm vs. 69% of patients in the placebo arm). Adverse events at least grade 3 in severity were also comparable (11% in both treatment arms).

Table 11.1:

<table>
<thead>
<tr>
<th>n (%)</th>
<th>TMC207/BR</th>
<th>Placebo/BR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Investigational</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>Treatment Phase</td>
<td>Treatment Phase</td>
</tr>
<tr>
<td></td>
<td>N = 79</td>
<td>N = 79</td>
</tr>
<tr>
<td>Any AE</td>
<td>77 (97.3)</td>
<td>78 (98.7)</td>
</tr>
<tr>
<td>Any AE at least possibly related to TMC207/placebo</td>
<td>55 (69.6)</td>
<td>55 (69.6)</td>
</tr>
<tr>
<td>Any AE at least possibly related to the BR</td>
<td>73 (92.4)</td>
<td>74 (93.7)</td>
</tr>
<tr>
<td>Any AE resulting in death(^a)</td>
<td>1 (1.3)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>6 (7.6)</td>
<td>19 (24.1)</td>
</tr>
<tr>
<td>Any SAE at least possibly related to TMC207/placebo</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Any AE leading to a permanent stop of</td>
<td>4 (5.1)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>TMC207/placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE leading to a permanent stop of TMC207/placebo and at least possibly related to TMC207/placebo</td>
<td>3 (3.8)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Any AE at least grade 2</td>
<td>51 (64.6)</td>
<td>63 (79.7)</td>
</tr>
<tr>
<td>Any AE at least grade 3</td>
<td>22 (27.8)</td>
<td>34 (43.6)</td>
</tr>
<tr>
<td>Any AE of grade 4</td>
<td>5 (6.3)</td>
<td>11 (13.5)</td>
</tr>
<tr>
<td>Any AE at least possibly related to TMC207/placebo and at least grade 2</td>
<td>24 (30.4)</td>
<td>24 (30.4)</td>
</tr>
<tr>
<td>Any AE at least possibly related to TMC207/placebo and at least grade 3</td>
<td>8 (10.1)</td>
<td>9 (11.4)</td>
</tr>
<tr>
<td>Any AE of at least grade 3 or leading to a permanent stop of any study medication or an SAE</td>
<td>26 (32.9)</td>
<td>38 (48.1)</td>
</tr>
</tbody>
</table>

\(^a\) One subject died due to an SAE starting during follow-up.

Reference

\(^1\)Mycobutin (rifabutin) capsule (human prescription drug label). Available at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3c1a6613-bdd3-4261-93b3-d7f5ce09064b.
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 will be implemented globally. Medicine costs will be lowest in the Global Drug Facility-sourced countries 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.

Bedaquiline will be first available in the United States of America. US pricing information will be established contingent on FDA approval (for which target action is date 29 December 2012) and that information can be provided to the Expert Committee thereafter.

Local Marketing authorisation in Russia and China is expected in the third or the fourth quarter of 2013 and in the fourth quarter of 2013 in South Africa (pending confirmation of fast track approval) after which costs of the medicines will be established.

For most patients with MDR-TB, an intensive phase of 8 months and total treatment duration of 20 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.

1 WHO. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update.

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)

Cost per case treated:
In a placebo-controlled clinical trial to evaluate the impact of bedaquiline when added to standard of care (SOC) in MDR-TB, bedaquiline demonstrated both significantly improved cure rates, significantly earlier suppression (sputum conversion) and improved and more sustained long-term response vs. SOC (see Sections 10 and 11).

A simple state-space economic model was used to evaluate the costs and cost-effectiveness of adding bedaquiline to the SOC regimen, based on costs and patterns of treatment in the US. The model included cost of medications, in-patient and ambulatory care, diagnostics and monitoring, as well as management of treatment failures. SOC was assumed to be that patients received an intensive drug regimen in an in-patient setting for up to 6 months (for 75% of patients, based on expert opinion of physicians treating MDR-TB in the US), but earlier suppression could lead to early release to an out-patient setting. Based on the clinical
trial results, bedaquiline was assumed to reduce this in-patient phase by 34 days on average. The continuation phase of treatment began 4 months after two successive negative sputum culture conversions, and was assumed to last 12 months, using a less intensive drug regimen and always done in an out-patient setting. Two different alternatives were considered for management of treatment failures, that they might continue to receive intensive treatment, in a hospitalized setting, for up to two years, or that following a surgical intervention, they would achieve a cure after a further round of intensive drug therapy. The cost of bedaquiline was set to $US 0 to estimate value. A separate transmission impact analysis was performed (see below).

In the base case, the average cost savings from the addition of bedaquiline to MDR-TB treatment vs. SOC was $US 181,523. The model showed sensitivity to the rate of hospitalization during intensive treatment phase, but it continued to predict significant cost savings in sensitivity analyses. If surgical management of treatment failures was factored in, the average cost savings reduced to $US 86,254. When varying to assume no improvement in time to suppression, cost savings were $US 130,476. With 25% hospitalization during intensive phase, cost savings were $US 67,172. In summary, the clinical efficacy of bedaquiline results in favorable economic cost savings to the healthcare system and MDR-TB treatment regimes.

Costs per new infections via transmission averted:
Given the high cost of MDR-TB treatment, there are significant cost-savings from a reduction in MDR-TB transmission. The value of bedaquiline was also evaluated in terms of a reduction of transmission of MDR-TB based on a 2010 US cohort of 88 MDR-TB patients over a one year time-horizon, assuming that a patient with active MDR-TB can infect 0.12 patients per month. Bedaquiline was predicted to prevent 18 (13–24) new infections per year in the US versus SOC. Using the US Center of Disease Control (CDC) estimate of $US 241,500 to treat a case of MDR-TB in the US, the use of bedaquiline would lead to the cost savings of $4.3M ($3.1M - $5.7M) per year.

If an infectious MDR-TB patient infected only 0.015 individuals (instead of the predicted 18 individuals) during the course of an infectious year, the value of the medicine would reach a threshold of $US 50 000 in the US healthcare context.

Costs per QALY gained:
Factoring in long-term health outcomes, the time period spent in various treatment states and the quality of life in those treatment states, this intervention has a negative cost per QALY (both cost-savings and additional health benefits) unless the price per course were close to $US 100,000. Moreover, these costs per QALY do not reflect the cost savings or QALY benefits of reduced transmission of the disease.
<table>
<thead>
<tr>
<th>Price per course</th>
<th>Cost per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>$US 100</td>
<td>-88,375</td>
</tr>
<tr>
<td>$US 1,000</td>
<td>-87,452</td>
</tr>
<tr>
<td>$US 10,000</td>
<td>-78,220</td>
</tr>
<tr>
<td>$US 100,000</td>
<td>14,101</td>
</tr>
<tr>
<td>$US 133,478</td>
<td>48,442 (US GDP 2011)</td>
</tr>
</tbody>
</table>

2CDC 2009 MMWR 58

Cost and cost-effectiveness in a developing country setting:
We applied the same state-space economic model to the Peruvian setting, and used economic inputs based on a recent systematic review of the cost and cost effectiveness of treatment for MDR-TB1, as well as drug costs derived from the 2nd Meeting of the Global GLC Committee, WHO, 28–29 February 2012 Meeting Report2.

In the Peruvian setting, for a patient who follows a standard course of treatment (8 months of intensive therapy followed by 12 months of continuation therapy, per the WHO guidelines3), we assumed, based on the data presented in Fitzpatrick and Floyd4, that 30% (averaged across patients) of the intensive treatment phase time prior to conversion is spent in hospital, and the remainder is in the community setting.

The cost per standard patient was estimated to be $US 15,361; but patients who relapse and have to be retreated cost on average $US 27,402, with costs of $US 38,735 for patients who fail to respond to treatment (using a two-year time horizon).

Adding bedaquiline to the treatment regimen, and accounting for the faster time to cure, increase in success rates and reduction in relapse rates, results in a cost savings $US 4,353, of which $US 2,237 is in savings on the drug regimen, and $US 2,117 is saved on treatment costs.

The added benefit of reduced transmission results in a net savings of $US 15,021.

The cost per QALY gained is $US 19,874; adding bedaquiline to the treatment regimen results in an improvement in QALYs and a reduction in costs. For the cost per QALY gained to be 0, the cost of treatment with bedaquiline would have to be $US 19,874.
1. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well).

Regulatory submissions for bedaquiline are prioritized based on stringent regulatory approvals (FDA, EMA), accelerated approvals and treated burden of disease.

The “PDUFA” date, i.e., the deadline for review of bedaquiline 100 mg tablets New Drug Application by the FDA, is on 29 December 2012.

The expected date for Marketing Authorization decision for bedaquiline 100 mg from EMA is Q4 2013.

Local Marketing authorisation in Russia and China is expected in Q3–Q4 2013 and in South Africa Q4 2013.

The product will be manufactured in India. We anticipate filing for regulatory approval in India after FDA approval (Q2 2013).

In addition to these regulatory filings, we will prioritize regulatory filings in 2013 and 2014 based on reported (to WHO) numbers of MDR-TB treatments.


None

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

<table>
<thead>
<tr>
<th>bedaquiline</th>
<th>Tablet: 100 mg</th>
</tr>
</thead>
</table>