An Activist's Guide to

BEDAQUILINE (Sirturo)

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I. Introduction

New drugs are urgently needed to get to zero deaths, zero new infections, and zero stigma and suffering from tuberculosis (TB). While TB has been curable for decades, existing drugs have to be taken for months or even years. Even then, cure rates can range from 30% to 80% for cases of drug-resistant TB, depending on the extent of resistance.[1,2] People with drug-resistant TB must resort to second-line drugs, which are more toxic, less effective, and more expensive. However, in December 2012, a new drug called bedaquiline was approved for the treatment of multidrug-resistant TB (MDR-TB).[3] Bedaquiline (also known by its trade name, Sirturo, or as TMC207) is the first new drug from a new drug class to treat TB to be approved by the United States Food and Drug Administration (FDA) in over 40 years. This guide highlights important safety and efficacy data reported thus far and offers advocacy recommendations for activists to take forward.

II. The efficacy of bedaquiline

FDA approval of bedaquiline was based primarily on two phase II studies involving 440 people with drug-resistant TB. These studies found that:

- Bedaquiline, when given with other existing MDR-TB drugs, increased the proportion of people whose sputum cultures converted after two and after six months of treatment (meaning there was no longer live *M. tuberculosis*, the bacteria that cause TB disease, in their phlegm).[4] This is a critical sign that treatment is working (see figure 1).

- Bedaquiline, when given with other existing MDR-TB drugs, reduced the amount of time to sputum culture conversion,[5] meaning it may be able to shorten treatment duration (see figure 2).

- In a very limited analysis, fewer individuals developed resistance to the other anti-TB drugs in their treatment regimen when bedaquiline was included.[6] This means that bedaquiline could be helpful in preventing the emergence of further drug resistance in MDR-TB patients as long as there are sufficient other background drugs in the regimen to which the TB organism is susceptible.

While only a few hundred people have taken bedaquiline so far, it appears that when added to regimens containing older drugs, bedaquiline is very effective at treating MDR-TB.

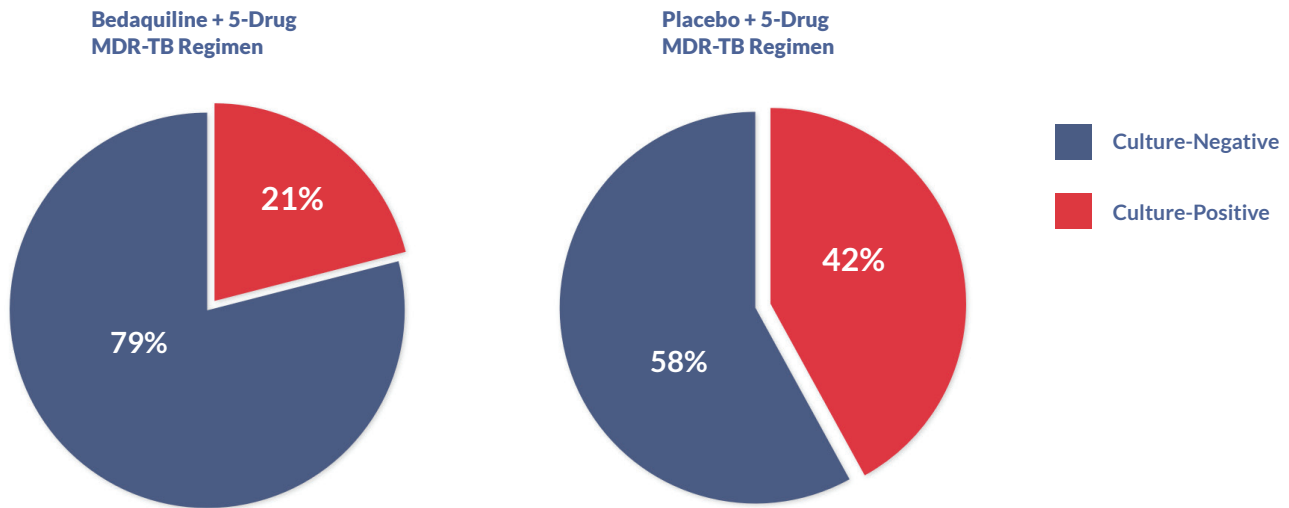## Key definitions and acronyms

TB: tuberculosis

MDR-TB: multidrug-resistant TB; or TB resistant to at least isoniazid and rifampicin, the two most powerful existing TB drugs, which are used as part of the four-drug first-line therapy.

Pre-XDR-TB: pre-extensively drug-resistant TB; or MDR-TB that is resistant to either a second-line injectable drug (amikacin, kanamycin, or capreomycin), or a fluoroquinolone.

XDR-TB: extensively drug-resistant TB; or MDR-TB that is also resistant to a fluoroquinolone and at least one injectable second-line drug.

Percent of Patients Whose Cultures Are TB-Negative After 24 Weeks in Phase II (Study C208)

**Bedaquiline + 5-Drug
MDR-TB Regimen**

**Placebo + 5-Drug
MDR-TB Regimen**

21%

79%

42%

58%

■ **Culture-Negative**

■ **Culture-Positive**

Note: The preferred five-drug MDR-TB background regimen consisted of ethionamide, pyrazinamide, ofloxacin, kanamycin, and either terizidone or cycloserine. Changes in the background regimen occurred over time due to drug susceptibility results, side effects, and drug shortages at sites that led to switches within the same drug class.

Source: Janssen Pharmaceutical Companies. Anti-infective drugs advisory committee meeting briefing document TMC207 (bedaquiline). Treatment of patients with MDR-TB. NDA 204-384. 2012 November 28. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf. (Accessed 2013 February 12)

III. The safety of bedaquiline

Side effects and mortality

Most drugs used to treat MDR-TB can cause serious side effects—and this includes bedaquiline. Preclinical and clinical studies show that bedaquiline may cause

- **QT prolongation,** a disturbance in the heart's electrical activity that could potentially lead to serious (and sometimes fatal) rhythm disturbances;

- **hyperuricemia** (a condition that can lead to *gout*), a buildup of uric acid in the blood, which can lead to swelling in the joints;

- **phospholipidosis,** the accumulation of phospholipids in the body's tissues;

- **elevated aminotransferases,** increased liver enzymes in the blood, which indicates potential liver damage; and

- **nausea, joint pain, headache, chest pain,** and **hemoptysis** (coughing up blood).[7]
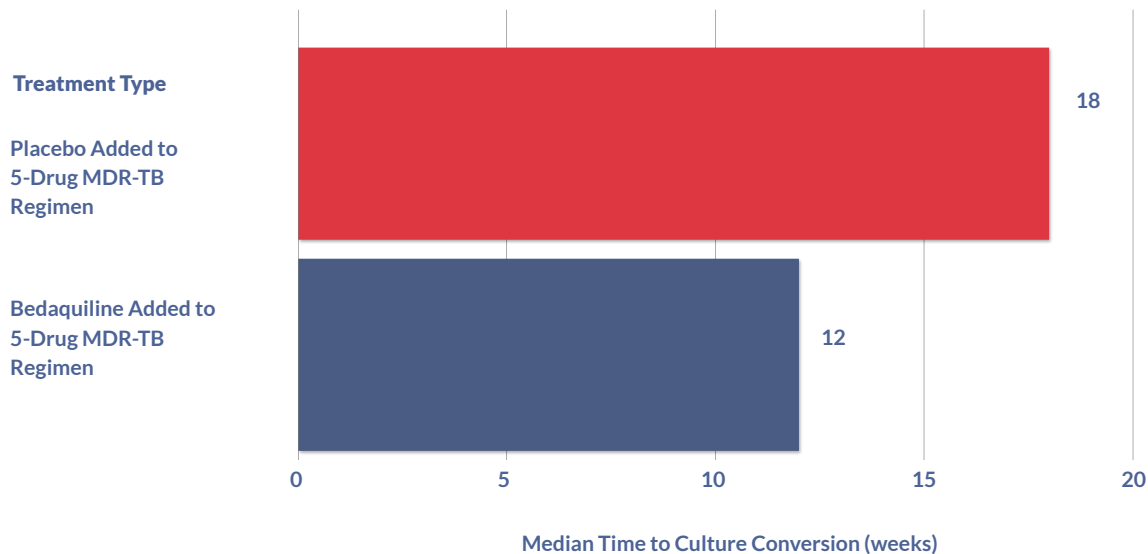
One study found that 10 out of 79 (13%) patients who took bedaquiline and other drugs died, compared with only 2 out of 81 (2%) who took other drugs plus the placebo. There was no common cause of death in those who died in the bedaquiline arm and all but one death occurred long after stopping bedaquiline, meaning it remains unclear if the deaths were directly related to the use of bedaquiline.[8] Though the overall number of people who have received the drug in clinical trials remains small, the increased mortality raises a major concern about bedaquiline's safety.

Long half-life

Bedaquiline has a long terminal half-life (about five and a half months), meaning that it stays in the body a long time.[9] This allows for dosing every other day (after an initial two weeks of daily dosing). However, as other anti-TB drugs are taken daily, bedaquiline could complicate dosing schedules for people with TB and their clinicians and caregivers. Bedaquiline's long half-life may also mean that people taking it are exposed to its side effects longer. Finally, because bedaquiline remains in

Median Time to Culture Conversion (from TB-Positive to TB-Negative) in Phase II (Study C208)

Treatment Type

Placebo Added to 5-Drug MDR-TB Regimen — 18

Bedaquiline Added to 5-Drug MDR-TB Regimen — 12

Median Time to Culture Conversion (weeks)

Source: Janssen Pharmaceutical Companies. Anti-infective drugs advisory committee meeting briefing document TMC207 (bedaquiline). Treatment of patients with MDR-TB. NDA 204-384. 2012 November 28. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf. (Accessed 2013 February 12)

the body after other TB drugs have cleared, there may be the potential for resistance to bedaquiline to develop, particularly if therapy is discontinued prematurely (this would not be a problem if the patient were cured and all bacteria were killed).

Is bedaquiline safe and effective to use with other TB drugs?

All TB drugs need to be taken with other drugs to prevent drug resistance. Bedaquiline appears safe and effective to use with most TB drugs, though the drugs in the following list present special concerns.[10]

- **Rifampicin** and **rifapentine** (used to treat drug-sensitive TB). These drugs reduce the amount of bedaquiline in the body by about half.[11] Because of this, and because bedaquiline is approved for treatment of MDR-TB—which is by definition resistant to rifampicin—these drugs should not be used together.

- **Kanamycin.** Bedaquiline increases the amount of kanamycin (also used to treat MDR-TB) in the body by

half.[12] Dosing adjustments may be necessary to use the drugs together effectively.

- **Clofazimine** and **bedaquiline.** When taken together, these two drugs may increase the potential for heart problems, as they both cause QT prolongation.[13] This is also seen with drugs such as the fluoroquinolone moxifloxacin. Further safety studies and real-world combination follow-up in cases of patients who may need drugs with potentially overlapping toxicities such as these are needed.

- **Delamanid.** This new drug, in development for TB, also causes QT prolongation, and studies need to be done to see if bedaquiline and delamanid can be used together safely.[14]

Is bedaquiline safe and effective to use with HIV medicines?

Bedaquiline has not yet been studied in people with TB and HIV infection who are using antiretrovirals. For people who take HIV medications, particularly those who are coinfected with TB, drug-drug interactions are a very

important issue. Small studies giving uninfected people HIV medicines and a single dose of bedaquiline at a time show that

- **efavirenz,** based on a single-dose study and longer-term modeling, appears to reduce the amount of bedaquiline in the body by about half over time;[15]

- **lopinavir/ritonavir** (also known as Kaletra) slightly raises the amount of bedaquiline in the body; modeling needs to be done to see what the long-term effects would be;[16]

- **nevirapine** and bedaquiline do not appear to interact;[17] and

- **ketoconazole,** an antifungal commonly taken as part of HIV treatment, increases the amount of bedaquiline in the body. Patients taking both ketoconazole and bedaquiline had increased QT prolongation. As such, ketoconazole and bedaquiline should not be taken together for more than two weeks at a time unless the potential benefit outweighs the risk.[18]

A phase III trial of bedaquiline that is about to begin will include people with HIV who are on lopinavir/ritonavir and nevirapine, but not people who are taking efavirenz, though when more data on efavirenz and bedaquiline are available, this recommendation may change.[19]

Is bedaquiline safe for children?

Bedaquiline has not yet been tested in children. The first study to look at bedaquiline in children (both with and without HIV) will begin in early 2014;[20] this study should help determine the right dose of bedaquiline to use in children of different ages, and whether it is safe, but it will not be completed for a long time.

Is bedaquiline safe to give to pregnant or nursing women?

Like most new drugs, bedaquiline has not been tested in pregnant or nursing women. Studies in rats and rabbits showed no evidence that bedaquiline causes harm to the fetus; however, as animal studies cannot predict exactly what will happen in humans, the FDA advises that bedaquiline be used during pregnancy only if clearly needed.

Rat studies did show that bedaquiline is excreted in milk, and that offspring who feed on milk with bedaquiline in it have lower body weights. It is not known if bedaquiline is excreted in human breast milk. The FDA advises that decisions for nursing mothers should weigh the importance of the drug to the mother, and could include discontinuing the drug or discontinuing nursing.[21]

IV. Approval and Access

FDA approval

In December 2012, the U.S. Food and Drug Administration (FDA) granted bedaquiline accelerated approval for the treatment of pulmonary MDR-TB in adults based on the two-month and six-month sputum culture conversion advantage seen in those on bedaquiline plus background regimen vs. background alone. The recommended dose is 400 mg once daily for two weeks, followed by 200 mg three times per week for 22 weeks with food.[22]

The FDA can use the accelerated approval mechanism when there is a new drug for a serious or life-threatening illness, and there is some safety and efficacy information for that drug, but not full information about its long-term impact on disease or survival. Accelerated approval may be based on therapy-induced changes in a surrogate marker (such as CD4 count, viral load, or TB culture conversion) that is believed reasonably likely to predict clinical benefit (such as quicker cure, lower relapse, or reduced mortality). When the FDA gives accelerated approval, it requires further studies of the drug to verify its clinical benefit. The FDA can withdraw approval if a postmarketing study shows there was no clinical benefit, or if the drug sponsor does not perform the required studies.[23] In this case, the FDA approved bedaquiline under the condition that its sponsor, Janssen Infectious Diseases BVBA, complete several activities, including those listed in table 1.

Global access

The FDA approval allows for Janssen to market bedaquiline only within the United States; for other countries to gain access, Janssen must file an application with the corresponding regulatory authorities. To date, Janssen has submitted applications to the European Medicines Agency (EMA), the China State Food and Drug Administration, and the South African Medicines Control Council (MCC).[24] The World Health Organization (WHO) is currently evaluating the need to update the current MDR-TB treatment guidelines considering the additional benefit of bedaquiline; potential policy recommendations may be released by the second quarter of 2013.[25]

Selected Activities Required by FDA as a Condition of Approval

Requirement	Purpose	Deadline
Phase III trial and report	Assess long-term outcomes of treatment failure or relapse or death at least six months after all treatment is completed	2022
Patient registry	Assess the incidence of serious adverse events (including death) in all patients given bedaquiline in the U.S.	2019
Interaction trial with efavirenz	Determine a safe and effective regimen of bedaquiline and efavirenz when given to people with HIV and MDR-TB	2013

In the meantime, patients with few or no other treatment options may benefit from access to bedaquiline before its approval in their countries. Janssen has made the drug available for some patients with XDR- or pre-XDR-TB via skilled providers under highly controlled compassionate use programs and early access trials in several countries in Europe, the Americas, Africa, and Asia. However, in countries such as India, Moldova, and Nigeria, delays from regulatory authorities in granting an import license have prevented approved patients in need from accessing bedaquiline. Those interested in more information on how to access bedaquiline should contact Erica Lessem at Treatment Action Group (erica.lessem@treatmentactiongroup.org) on how to do so, and providers can contact Eveline van Wageningen-Evers at Janssen (ewageni@its.jnj.com).[26]

V. Take Action: Advocacy Messages

1. Bedaquiline is effective at fighting MDR-TB

Bedaquiline is clearly effective at treating MDR-TB. Most previous existing treatment options have not gone through rigorous clinical trials for TB, are not very effective, and have very severe side effects. Waiting for the results of phase III trials would likely mean delaying access to bedaquiline until 2022. MDR-TB patients, and especially those with pre-XDR and XDR-TB, need better options now. As such, advocates may want to advocate for the approval and use of bedaquiline in their countries now.

2. More research is necessary

While moving ahead with access, additional studies are needed to answer outstanding questions about bedaquiline's safety and optimal use. Specific studies of bedaquiline are also critical in populations such as children, people taking antiretrovirals, and people who use drugs and alcohol. Janssen must conduct the following studies (or facilitate their conduct by other research institutions) as soon as possible.

A phase III trial and patient registries. A larger-scale trial, and analyses of patients who have been given bedaquiline, are needed to fully establish bedaquiline's efficacy—particularly given the excess deaths in the bedaquiline arm of the phase IIb trial. These are a condition of FDA approval, but enforcement is often lax: an estimated one out of four trials that are a condition of accelerated approval never take place (or are not published), and yet the drugs remain approved.[27]

A pediatric study. Bedaquiline has not yet been studied in people under 18; its safety and proper dosing in children need to be established urgently to help improve treatment for children with drug-resistant TB. The International Maternal Pediatric Adolescent AIDS Clinical Trials network of the United States National Institutes of Health (NIH) is developing a protocol to study bedaquiline in children with MDR-TB with and without HIV. A child-friendly formulation for the drug is also necessary. Notably, under the FDA orphan-drug designation status to encourage investment in diseases such as TB, bedaquiline is exempt from normal pediatric develop-

ment requirements. Thus, advocates and other regulatory authorities have to maintain pressure on Janssen to fulfill these important obligations.

Studies in people who take HIV medicines. The FDA is requiring a drug-interaction trial of bedaquiline and efavirenz to determine safe and effective dosing of both drugs when they are given to people with MDR-TB and HIV. Follow-up studies and modeling or analysis of people on lopinavir/ritonavir (who will be included in the phase III trial) are also necessary to determine optimal dosing. Janssen should ensure that an adequate number of people living with HIV are enrolled in the phase III trial to ensure sufficient safety and efficacy data.

A safety study with delamanid. Delamanid is another new drug in late-stage development for MDR-TB, and is up for approval by the EMA in 2013. Bedaquiline and delamanid are likely to be used together once approved, but as they both cause QT prolongation, the safety of using them together needs to be determined. The NIH research networks can help conduct this study to address complications that arise from drug sponsors having to share data; however, Janssen and Otsuka (the developer of delamanid) must provide data in a timely fashion to enable this important collaboration. In general, new drugs to fight TB must be studied in combination in order to accelerate development timelines and inform their optimal use.

Research to inform the use of bedaquiline in people who use drugs and/or alcohol, and/or people co-infected with hepatitis B virus or hepatitis C virus. As bedaquiline may cause liver damage, further information is needed about its suitability for use in people who use alcohol or liver-damaging drugs, and/or are coinfected with hepatitis B or C virus. Additionally, research is needed to see if bedaquiline interacts with methadone and buprenorphine (both used to treat people with heroin dependency). Bedaquiline causes QT prolongation, which is a concern with methadone, and may also endanger patients who have cardiomyopathy (a heart condition that can be caused by heavy alcohol use). The overlap between TB and alcohol use, drug use, and hepatitis is high, particularly in Eastern Europe; use of bedaquiline in people who use drugs, alcohol, methadone, and/or buprenorphine urgently warrants further investigation.

3. Appropriate pricing and scale-up are needed to ensure timely approval and access

Swift regulatory review, approval, and binding of postmarketing commitments. Regulators must swiftly build their capacity to review new drugs, and enable approved drugs to quickly reach those in need. They also must ensure that they have the ability to enforce post-marketing commitments that may be a condition of approval. Furthermore, regulators should consider making bedaquiline (and other new drugs in development) available under controlled pre-approval access via compassionate use or expanded access programs. In addition to providing potentially lifesaving treatment to individuals at great risk, pre-approval access is a good trial run for demonstrating drug review and import capacity. Difficulties obtaining import licenses for bedaquiline under compassionate use in Botswana, India, Moldova, and Nigeria do not bode well for the abilities of the regulatory authorities in those countries to rapidly approve and obtain new drugs for routine use.

Affordable pricing. Janssen must price bedaquiline so that it is accessible. This means concessional pricing in both the low- and middle-income countries that disproportionately bear the burden of TB, and affordable pricing in low-incidence settings such as the United States where TB programs receive few resources.

Rollout capacity. Countries must also build their capacity to roll out new drugs for MDR-TB—currently, less than eight percent of those with MDR-TB receive proper treatment.[28] Once regulatory authorities approve a drug and its import, ministries of health, national treatment programs, pharmacies, and clinicians are responsible for its distribution and use. They need to scale up their infrastructure, human resources, and information systems to diagnose and treat MDR-TB patients appropriately and comprehensively, as well as to carefully monitor and follow up with patients on bedaquiline.

Advocates can take action by

- encouraging their local regulatory agencies to build capacity, to allow compassionate use of bedaquiline, and to invite Janssen to file in their countries for approval;

- advocating for fair pricing from Janssen; and

- holding Janssen accountable for fulfilling its commitment to completing research studies, and filling key research gaps.

Endnotes

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