AN ACTIVIST'S GUIDE TO BEDAQUILINE

TAG Treatment Action Group

DR-TB STAT

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This guide—updated from the original version put out by Treatment Action Group in 2013—summarizes updated efficacy, safety, and access information about bedaquiline, an essential medication in the treatment of **multidrug-resistant TB (MDR-TB)**. We wrote this guide to provide information about bedaquiline and its important role in MDR-TB treatment to people with MDR-TB, their caregivers, and their advocates so they can make informed choices and call for bedaquiline to be available, accessible, and affordable for all who need it.

I. BACKGROUND

In 2012, the U.S. Food and Drug Administration **conditionally approved** bedaquiline for the treatment of MDR-TB,[1] making it the first new drug from a new class in over 40 years. In June 2013, the World Health Organization (WHO) recommended bedaquiline for treating MDR-TB when there is resistance or intolerance to other TB medications.[2,3] In the five years since, almost 25,000 people, two-thirds of whom live in South Africa, have received bedaquiline.[4] Though there were initial concerns about bedaquiline's safety, a growing body of evidence has demonstrated that bedaquiline is both safe and effective—much more so than other MDR-TB drugs—leading the WHO to recommend it in 2018 as a core agent for the treatment of MDR-TB, and remove injectables as a core agent.[5] Injectable TB drugs are painful, cause serious side effects, including irreversible hearing loss, and lack evidence of efficacy against drug-resistant TB (in fact, kanamycin and capreomycin are linked to increased risk of treatment failure and death). Bedaquiline is the backbone of the first all-oral recommended MDR-TB regimens, marking an important shift toward making MDR-TB treatment more effective and acceptable to patients.[6]

II. THE EFFICACY OF BEDAQUILINE

Rigorous testing and programmatic use have demonstrated that bedaquiline is a strong drug for MDR-TB treatment. Key evidence for bedaquiline's **efficacy** includes:

- In the phase IIb clinical trial that led to bedaquiline's approval, including bedaquiline rather than a placebo in MDR-TB treatment regimens resulted in significantly faster times to **culture conversion**, higher rates of culture conversion, and higher cure rates.[7]
- Using bedaquiline in **pre-approval access programs** showed high rates of culture conversion at six months of treatment and high rates of treatment success (70-90%) when compared with patients who did not receive bedaquiline.[8,9,10]

KEY DEFINITIONS AND ACRONYMS

MDR-TB or multidrug-resistant TB, is 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. Since rapid testing is only available for rifampicin resistance, you may see people use rifampicin-resistant TB (RR-TB) and MDR-TB interchangeably.

CONDITIONAL APPROVAL means further studies are required within a certain timeframe; this was because phase III trials for bedaquiline were not completed (and are still not).

EFFICACY means how well a drug (or other intervention) works in a clinical trial, where conditions are usually more controlled than in regular patient care.

CULTURE CONVERSION means that the best test for whether TB treatment is working, called culture, goes from positive (there is TB growing) to negative (no growing TB can be detected). The rate of culture conversion and time to culture conversion are both measures of how well a drug is working, and they can be measured sooner than treatment success (finishing treatment without treatment failing or relapsing or death).

PRE-APPROVAL ACCESS PROGRAMS also called compassionate use or expanded access programs, allow clinicians to access a new treatment option such as bedaquiline for either individual or groups of patients prior to its registration in a given setting.

- A large study of more than 12,000 people who received treatment for MDR-TB between 2010 and 2015 from 25 different countries found that people who received bedaquiline had higher rates of treatment success and lower rates of death compared with people who did not receive bedaquiline.[11] Data from this study informed the 2018 WHO recommendation of bedaquiline-based therapy for all persons living with MDR-TB. Data on bedaquiline use in South Africa were pivotal to the WHO recommendation (see box).

SOUTH AFRICA'S AMBITIOUS BEDAQUILINE ROLLOUT SAVES LIVES AND GUIDES THE REST OF THE WORLD

South Africa leads the world in bedaquiline implementation, accounting for more than 66% of global bedaquiline use. A landmark study reviewed the records of 19,617 people treated for MDR-TB in South Africa from 2014 to 2016 and compared the outcomes of people treated with bedaquiline-containing regimens (1,016 people) with those of people treated without bedaquiline. People who received bedaquiline had a 41% increase in treatment success and were three times less likely to die during treatment than people who did not receive bedaquiline, even though they were often sicker at treatment start.[12] These outcomes led South Africa to declare that bedaquiline will be part of the initial treatment regimen for all people with MDR-TB in South Africa, replacing the highly toxic, less effective, and more harmful injectable agents.[13]

South Africa also directly assessed whether bedaquiline could replace the injectable agents. In another study, 146 persons who had hearing loss at treatment start, or who developed hearing loss during MDR-TB treatment, were offered bedaquiline instead of the injectable. The study found that, compared with 141 patients who were similar in other ways but did not receive bedaquiline, people who received bedaquiline instead of the injectable had significantly better treatment outcomes and substantially lower rates of being failed by treatment.[14]

III. THE SAFETY OF BEDAQUILINE

Like all drugs, bedaquiline has some risks. The benefits of bedaquiline far outweigh these risks for a majority of persons with MDR-TB, so bedaquiline is now recommended as a core agent for treating MDR-TB.

The main side effect of concern for bedaquiline is **QTc prolongation**. The QTc interval is a sign that the heart is ready to receive a signal to keep beating. The longer the interval, the longer it takes for the heart to receive another beat. Although not a problem itself, prolonged QTc can be a risk factor for developing **cardiac arrhythmias**, which can be associated with a high risk of death. Bedaquiline modestly prolongs the QTc interval. QTc prolongation is seen with hundreds of drugs, including other TB medicines (clofazimine, delamanid, and moxifloxacin). Early concerns about the safety of combining bedaquiline with other QTc-prolonging drugs do not appear to be as serious as previously thought.[16] However, there may be an increased risk of QTc prolongation if using more than three QTc-prolonging medicines together. Though few sudden deaths have been reported with bedaquiline, patients should have baseline and follow-up electrocardiogram (ECG) tests to make sure the

QTC PROLONGATION is a change in the electrical system of the heart.

CARDIAC ARRHYTHMIA is a heartbeat that is too fast, too slow, or irregular.

QTc interval is not prolonged (more than 450 milliseconds for men; more than 470 milliseconds for women). Whenever a person takes a drug that can prolong QTc, monitoring of potassium (and if low, supplementation of potassium and magnesium) should be routine care.

Initially, the phase IIb clinical trial that led to bedaquiline's approval several years ago raised a safety concern.[17] Treatment success rates in this trial were higher in those who received bedaquiline compared with placebo, but mortality was five times higher in the bedaquiline group (10 out of 79 patients [13%] who took bedaquiline died, compared with 2 out of 81 [2%] in the placebo group). None of the deaths were directly caused by bedaquiline. Still, this led to caution around bedaquiline's use and a recommendation for strict QTc monitoring.[18] The more recent South African programmatic data described above show bedaquiline's association with a lower death rate, countering the initial safety concern. In fact, serious side effects are much less frequent with bedaquiline than with other MDR-TB drugs, such as linezolid or the injectables.[19]

Other side effects reported with bedaquiline include liver inflammation, gastrointestinal problems, and joint pain, although these problems are common with MDR-TB treatment, and it can be difficult to know which drug was responsible for the side effect.

What about people living with HIV? Thousands of people living with HIV have taken bedaquiline with similar effectiveness and safety as in HIV-negative individuals. Bedaquiline cannot be given with certain antiretrovirals, most notably efavirenz: efavirenz cannot be used with bedaquiline since it can significantly decrease bedaquiline levels. Persons on efavirenz should be changed to nevirapine or ideally an integrase inhibitor while on bedaquiline.[20] Taking lopinavir/ritonavir increases bedaquiline levels, but it is not clear what this means for patients—no increase in adverse events was seen in patients who received bedaquiline with lopinavir/ritonavir.[21] Because protease inhibitors are commonly used for second-line antiretroviral therapy, lopinavir/ritonavir may be used with bedaquiline with appropriate ECG monitoring. It is essential that people on antiretrovirals when starting bedaquiline have their viral load tested prior to any changes in their antiretroviral regimen, as a high viral load can signal antiretroviral therapy failure and the need for careful regimen selection. Ketoconazole, an antifungal commonly taken as part of HIV treatment, increases the amount of bedaquiline in the body and can increase QT prolongation in people taking bedaquiline. Ketoconazole and bedaquiline should not be taken together for more than two weeks at a time unless the potential benefit outweighs the risk.[22]

BEDAQUILINE DOSING

Bedaquiline is available as 100 mg tablets. Bedaquiline is recommended at a dose of 400 mg once daily for the first 14 days of treatment, followed by 200 mg three days a week. Bedaquiline is dosed this way because it binds to fatty tissue in the body and thus can take some time to build up to the right level. Once this level is reached, bedaquiline stays in the body for a long time (i.e., it has a long half-life, about six months), so a lower dose can be used for the rest of treatment.

The best duration for giving bedaquiline along with other effective drugs is unknown; studies are ongoing. The WHO recommends bedaquiline for 24 weeks on the basis of the data so far. But bedaquiline has been given for longer with good outcomes and with no increase in reported adverse events.[15] Many patients need bedaquiline for longer than six months, which clinical experience suggests is safe.

What about people being treated for hepatitis C virus (HCV)? Early experience suggests bedaquiline can be safely taken with direct-acting antivirals to treat hepatitis C. However, more research is needed to confirm the safety of giving bedaquiline with HCV treatment.

What about children? There is growing experience using bedaquiline in adolescents and children.[23] Adolescents, who metabolize (process) drugs similarly to adults, can be given bedaquiline. Although research on younger children is needed and is underway,[24] evidence so far supports the use of bedaquiline in children at half the adult dose (200 mg daily for 14 days followed by 100 mg three times a week). A recent study showed that crushing bedaquiline tablets and mixing them with water results in similar drug levels to whole tablets; smaller children who cannot swallow tablets can be given bedaquiline this way.[25] While research is ongoing and WHO guidance is pending, the benefits of using bedaquiline in children outweigh the risks. Age should not be used as a reason to deny a person with MDR-TB, including a child or adolescent, access to bedaquiline.

What about pregnant individuals? Bedaquiline can be used during pregnancy, and animal studies show no safety concerns.[26] In fact, bedaquiline is likely to be one of the safest drugs to use when treating MDR-TB in pregnancy. Though there are limited data on its use during pregnancy, it is the preferred drug for people with MDR-TB who are or who become pregnant. Breast milk can contain bedaquiline. Although the amount of drug passed on to a breastfed child is likely small, there is still a risk for side effects in the infant. In settings where safe feeding alternatives are not available or bedaquiline needs to be continued in order to ensure an effective MDR-TB regimen, breastfeeding may still be continued.

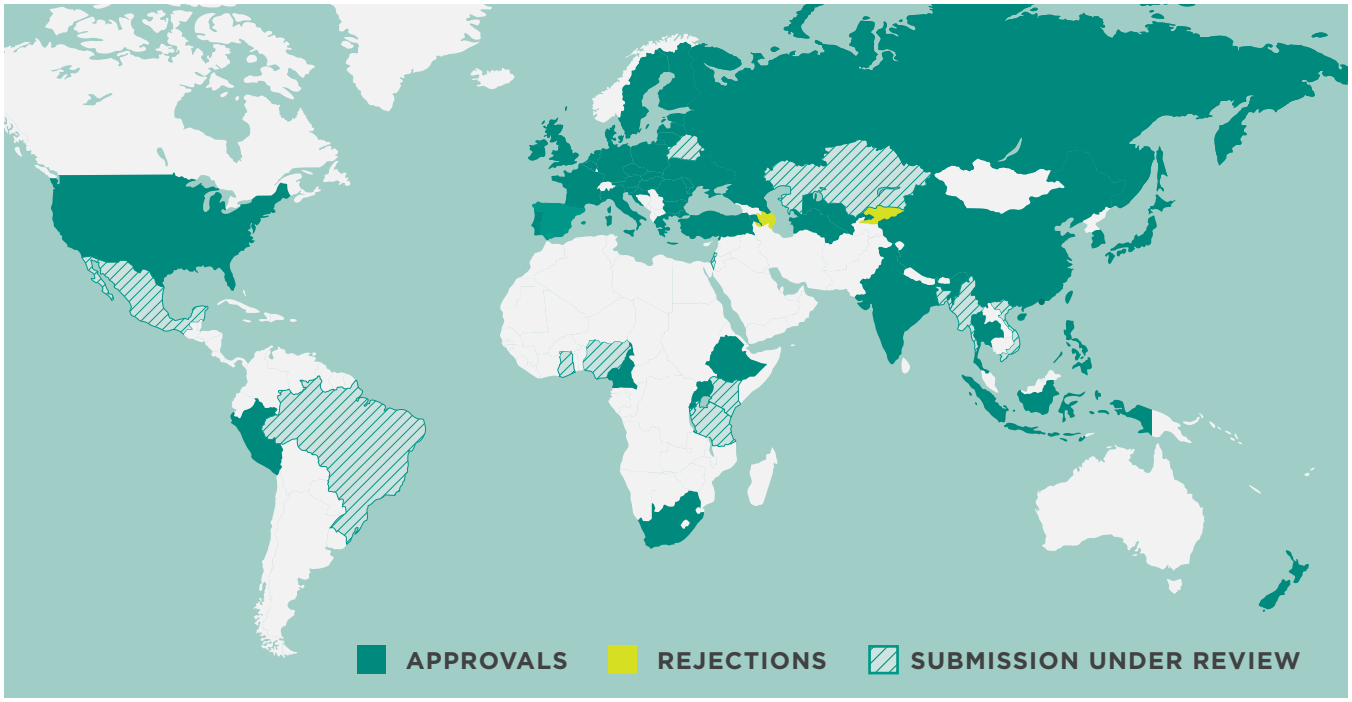
What about people who use drugs or alcohol? Because bedaquiline—like many other TB drugs—may have some side effects on the liver, it is best to avoid drinking alcohol while on TB treatment. Bedaquiline's QT prolongation may be a special risk for patients with cardiomyopathy (a heart condition that can be caused by heavy alcohol use). However, drinking alcohol—or using drugs or opioid substitution therapy—should never be a reason for denying access to bedaquiline. Research is needed to see whether bedaquiline interacts with methadone and buprenorphine (used to treat people with opioid dependency). Methadone also prolongs QTc, so, as noted, caution should be used with giving multiple QT-prolonging drugs together.

IV. ACCESS

Bedaquiline is manufactured by Janssen, a division of the company Johnson & Johnson. Bedaquiline is available from the Stop TB Partnership's Global Drug Facility and currently has a three-year shelf life. It can be imported under waiver or emergency mechanisms in settings where it is not yet registered; the Global Drug Facility can assist with importation requirements. Regardless of funding sources, treatment programs can order bedaquiline via the Global Drug Facility by contacting bdq@stoptb.org. If you are an individual hoping to seek bedaquiline for yourself, a patient, or loved one, please contact communications@treatmentactiongroup.org.

The below map indicates in which countries bedaquiline is registered for use, or where approval is pending. Bedaquiline's approval is based on a phase IIb trial that had a small number of participants, so approval is conditional on the completion of additional research, such as a phase III clinical trial.

MAP: BEDAQUILINE REGISTRATIONS AND SUBMISSIONS



APPROVALS

United States (2012)
European Union (2014)
Japan (2018)
Russia (2013)
Philippines (2014)
South Africa (2014)
Peru (2014)
India (2015)
Uzbekistan (2015)
China (2016)
Moldova (2017)
Thailand (2017)
Ethiopia (2018)
Indonesia (2018)
South Korea (2014)
Turkmenistan (2014)
Armenia (2015)
New Zealand (2016)
Hong Kong (2016)
Taiwan (2016)
Turkey (2017)
Rwanda (2017)
Uganda (2018)
Cameroon (2018)
Ukraine (2018)

REJECTIONS

Kyrgyzstan (2015
Azerbaijan (2015)

SUBMISSION UNDER REVIEW

Bangladesh (2015)
Belarus (2018)
Mexico (2015)
Nigeria (2016)
Brazil (2017)
Tanzania (2016)
Burundi (2016)
Ghana (2016)
Kenya (2016)
Kazakhstan (2018)
Myanmar (2018)
Israel (2018)
Vietnam (2018)

Pricing

In 2015, the U.S. Agency for International Development (USAID) in partnership with Janssen announced a donation program of 30,000 free courses of bedaquiline available to most countries qualifying for Global Fund support. By July 2018, all 30,000 courses were claimed, at which point USAID announced an additional 30,000 courses would be available. After March 2019 (or when those 30,000 courses are all used, whichever is earlier), programs can purchase bedaquiline from the Global Drug Facility for US$400 for a six-month course (188 tablets, $67 per month).[27] Researchers calculate that bedaquiline could be produced and sold at a profit at just $16 per month (though at larger volumes than are currently sold).[28] Activists have called on Johnson & Johnson to lower the price of bedaquiline to $32 per month for all countries and commit to further transparent, volume-based targets negotiated by the global TB response community.[29]

V. TAKE ACTION: ADVOCACY MESSAGES

1. **Bedaquiline is an essential medicine and a core MDR-TB drug**. Almost all people with MDR-TB should receive bedaquiline from the start of treatment. Bedaquiline should be given instead of injectable agents; can be taken with other newer MDR-TB drugs such as delamanid, linezolid, and clofazimine; and can be safely administered for longer than 24 weeks. Bedaquiline can be given to children, to pregnant individuals, and to people with HIV on compatible antiretroviral regimens. *Advocates should ensure their national TB treatment guidelines include bedaquiline as part of the core regimen for MDR-TB, including in children, pregnant individuals, people with HIV, people on delamanid, and people who need bedaquiline for more than six months.*

2. **Safety monitoring matters.** All persons on bedaquiline should have an ECG done at baseline and at routine intervals thereafter to monitor for QTc prolongation. Potassium levels should be monitored and corrected through supplements, as well. Scaling up the use of bedaquiline is a unique opportunity to strengthen the existing care and management of people on MDR-TB treatment. *Activists should play a watchdog role to ensure regular monitoring and supplementation are included in guidelines and available free of charge to all with MDR-TB.*

3. **Drug susceptibility testing matters.** All people in need of evaluation for TB have the right to universal drug susceptibility testing through the use of GeneXpert MTB/RIF (or MTB/RIF Ultra), which tests for rifampicin resistance; the WHO recommends that resistance to rifampicin be treated as MDR-TB. All persons diagnosed with rifampicin resistance or MDR-TB should have further testing for additional resistance to second-line TB drugs through a line probe assay and culture.Finally, people taking bedaquiline should have access to drug susceptibility testing; this is especially important for people who are not improving on treatment. The level of bedaquiline needed to stop the growth of TB (called a critical concentration) has been established for both solid and liquid culture.[30] But most countries are not testing at all yet for bedaquiline resistance. Labs should introduce routine bedaquiline testing with faster liquid culture, both for patient care and for monitoring levels of bedaquiline resistance in the population. *Activists should call on their national TB program to ensure universal drug susceptibility testing, to build lab capacity for bedaquiline susceptibility testing, and, in the meantime, to collect and save selected samples for testing later on.*

4. **Additional research is required.** There is still a need for additional research to optimize bedaquiline's use in vulnerable populations, to assess the role of bedaquiline in treatment shortening for MDR-TB, and to determine the best combination of drugs. *Activists should hold Janssen accountable for fulfilling its commitment to completing research studies and filling key research gaps, as well as call for increased public funding for TB research.*

5. **Equitable access to bedaquiline is a human rights imperative.** Bedaquiline is now recommended as a core drug in the treatment of MDR-TB, but many countries and programs have treated only a very small proportion of people who could benefit from bedaquiline with this medication. This may be due to lack of registration and difficulty with importation or to high pricing for countries unable to access the current (and now ending) drug donation program. Additionally, strong leadership and political will at the country level is essential to promote access to recent and future innovations in TB diagnosis and treatment. To ensure there are no barriers to obtaining and using this life-saving medication, advocates should demand their governments provide bedaquiline to all people with MDR-TB. *Activists should also call for fair pricing and worldwide bedaquiline registration from Janssen. If working in a country where registration is pending or rejected, activists should demand the regulatory authority approve bedaquiline.*

6. **Experience sharing is critical to expanding access.** Globally, bedaquiline uptake has not kept pace with need, and expertise in using this medication is concentrated in a small number of countries and implementing organizations. Optimal use of the drug is necessary to ensure the best possible outcomes for patients and for programs. Technical assistance for all countries must be led by providers who have experience using bedaquiline. *Activists should ask technical assistance providers and WHO offices to ensure experienced bedaquiline providers are leading technical assistance and support activities in the country/region.*

7. **The patient is always at the center of our efforts.** Patient education and informed choice regarding TB treatment and the use of bedaquiline is essential to upholding human rights. Ongoing education and support throughout treatment for all patients and their families, whether receiving bedaquiline or not, improve outcomes and are as—or more—important than the drugs the patients receive. *Advocates should assist with community education to raise awareness of bedaquiline, ensure that every patient is active in the care and treatment they receive, and prioritize inclusion of treatment support strategies in the programmatic management of MDR-TB.*

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