

TB Elimination

Treatment of Multidrug-Resistant Tuberculosis: Bedaquiline

Introduction

Bedaquiline fumarate (Sirturo™) is approved by the U.S. Food and Drug Administration (FDA) for use as part of a combination therapy in adults with pulmonary multidrug-resistant tuberculosis (MDR TB) when an effective treatment regimen cannot otherwise be provided.

The effectiveness and safety of this drug in different patient populations is unknown at this time.

For more detailed information, refer to the *Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo™) for the Treatment of Multidrug-Resistant Tuberculosis*.

www.cdc.gov/mmwr/pdf/rr/rr6209.pdf

Dosage and Administration

Due to the potential for serious adverse events, bedaquiline is not recommended for all MDR TB patients.

Patients treated with bedaquiline should be managed by, or in close consultation with, local health departments and experts in the management of drug-resistant TB.

Bedaquiline may be used to treat adults (> 18 years) with a confirmed diagnosis of pulmonary MDR TB.

CAUTION: Bedaquiline may be considered for children, HIV-infected persons, pregnant women, persons with extrapulmonary TB, and persons with co-morbid conditions on concomitant medications when an effective treatment regimen cannot otherwise be provided. Further study is required before general use of bedaquiline can be recommended in these populations.

Expert Clinical Consultation

Medical consultation is available through some state TB programs or CDC's TB Regional Training and Medical Consultation Centers (RTMCCs).

Visit the CDC website to obtain contact information for each RTMCC.

www.cdc.gov/tb/education/rtmc/default.htm

Visit the CDC website to obtain contact information for each state TB program office.

www.cdc.gov/tb/links/tboffices.htm

Recommended Dose

The recommended dose of bedaquiline for the treatment of pulmonary MDR TB in adults is:

- Weeks 1 – 2: 400 mg (4 tablets of 100 mg) given orally, once daily
- Weeks 3 – 24: 200 mg (2 tablets of 100 mg) three times per week, for a total dose of 600 mg per week

Initiation and Discontinuation

Bedaquiline is to be used for a period of 24 weeks.

- Bedaquiline may be used on a case-by-case basis for durations longer than 24 weeks when treatment options are limited.

This drug has a half-life of 4-5 months. Consider discontinuing bedaquiline 4-5 months prior to discontinuing other drugs in the treatment regimen to reduce or avoid an extended period of exposure to low levels of bedaquiline as a single drug and subsequent acquired resistance.

Administration

All doses should be used in combination with at least three other anti-TB drugs to which the patient's MDR TB isolate has been shown to be susceptible through laboratory testing.

Each dose should only be given by directly observed therapy (DOT) and with case management strategies to ensure treatment adherence. Each dose should be taken with food to maximize drug absorption.

Missed Doses

If a dose is missed during the first 2 weeks of treatment, patients should not be given the missed dose but should continue the usual dosing schedule. From Week 3 onwards, if a 200 mg dose is missed, patients should be given the missed dose as soon as possible, and then resume the 3 times a week regimen. Do not exceed 600 mg in a 7-day period of time.

Adverse Reactions

To date, adverse drug reactions associated with bedaquiline include:

- Nausea / Vomiting
- Dizziness
- Headache
- Hemoptysis
- Increased blood amylase
- Increased serum transaminases
- Rash
- Arthralgia (joint pain) / Myalgia (muscle pain)
- Chest pain
- Anorexia, fatigue, dark or cola-colored urine, jaundice

Patient Counseling

Patients should be advised:

- To eat food before taking bedaquiline
- To abstain from alcohol and other hepatotoxic drugs
- To report any signs and symptoms of adverse drug reactions to their health care provider
- Of the potential benefits and harms of bedaquiline
- That treatment non-adherence could result in treatment failure, relapse, or acquired drug resistance

Drug Interactions

Bedaquiline is metabolized through the cytochrome P450 (CYP) system. Co-administration with rifamycins (e.g., rifampin, rifapentine, and rifabutin) or other strong CYP3A4 inducers should be avoided.

Among the limited studies to date, no significant pharmacokinetic interactions have been observed between bedaquiline and the anti-TB drugs isoniazid, pyrazinamide, ethambutol, kanamycin, ofloxacin, or cycloserine.

Patient Monitoring

Monitoring for Cardiac Toxicity

Bedaquiline can affect the heart's electrical activity, which could lead to an abnormal and potentially fatal heart rhythm. Patients should be monitored for symptoms of cardiac toxicity and by electrocardiogram (ECG).

- Serum potassium, calcium, and magnesium should be obtained at baseline and whenever clinically indicated, especially if QTcF prolongation is detected.
- ECG should be obtained at baseline and repeated at least 2, 12, and 24 weeks after treatment is started.
- Weekly ECGs are recommended for persons prescribed bedaquiline and (1) other QTcF prolonging drugs including fluorquinolones, macrolide antibacterial drugs, and clofazimine; (2) have a history of *Torsade de Pointes*, congenital long QTcF syndrome, hypothyroidism and bradyarrhythmias, or uncompensated heart failure; or (3) have serum calcium, magnesium, or potassium levels below the lower limits of normal.
- If syncope occurs, obtain an ECG to evaluate for QTcF prolongation.

Monitoring for Hepatotoxicity

Hepatic-related adverse drug reactions have been reported with the use of bedaquiline. Patients' aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase should be tested at baseline, monthly, and if symptomatic.

Monitoring for Renal Toxicity

Bedaquiline does not require dosage adjustment in patients with mild to moderate renal impairment (not requiring dialysis). Use caution when administering bedaquiline to patients with severe renal impairment requiring dialysis. Serum drug levels in patients with renal impairment should be considered.

Therapeutic Drug Monitoring

If bedaquiline is given with rifamycins or any other drugs that induce or suppress CYP3A4, monitoring of serum drug levels should be performed to ensure adequate therapy and minimize the risk of acquired drug resistance.

Microbiologic Monitoring

Treatment should be accompanied by microbiologic monitoring with one sputum specimen submitted for culture monthly throughout and at the end of treatment, even after conversion to negative culture.

Monitoring for Additional Side Effects

Patients should also be assessed weekly for nausea, headache, hemoptysis, chest pain, arthralgia, and rash. Monitoring for additional side effects should be tailored to the other drugs used to treat the patient's MDR TB.

Patient Registry and Surveillance of Drug Resistance

As required by the FDA, a registry for persons treated with bedaquiline will be maintained by Janssen Therapeutics to track patient outcomes, adverse reactions, laboratory testing results, use of concomitant medications, and presence of other comorbid conditions. This registry will collect data prospectively on all patients started on bedaquiline.

Any monthly specimen that grows *M. tuberculosis*, including one before treatment initiation with bedaquiline, should be referred to a laboratory for surveillance of bedaquiline resistance in consultation with the state public health laboratory. CDC will assist in identifying a laboratory that can perform bedaquiline susceptibility testing.

Suspected adverse reactions (i.e., any adverse event for which there is a reasonable possibility that the drug caused the adverse event) and serious adverse events (i.e., any adverse event which results in death, hospitalization, permanent disability, or a life-threatening situation) should be reported to Janssen Therapeutics (1-800-526-7736), the FDA (1-800-332-1088 or www.fda.gov/medwatch), and to CDC's Emergency Operations Center (1-770-488-7100).

Additional Information

1. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo™) for the Treatment of Multidrug-Resistant Tuberculosis. MMWR 2013; 62 (No. 9): www.cdc.gov/mmwr/pdf/rr/rr6209.pdf
2. Janssen Therapeutics. Sirturo™ Webpage www.sirturo.com/
3. U.S. Food and Drug Administration. SIRTURO™ (bedaquiline) Tablets label. US Food and Drug Administration website. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm368240.htm>.