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BEDAQUILINE AS POTENT PULMONARY MULTIDRUG RESISTANT TUBERCULOSIS BACTERIA

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ABSTRACT

Multidrug-resistant TB (MDR TB) is caused by TB bacteria that are resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease. TB experts should be consulted in the treatment of MDR TB.

KEYWORDS: MDR-TB, Bacteria, DOT, Mycolic acid, Bacillus.

INTRODUCTION

Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis*. The bacteria usually attack the lungs, but TB bacteria can attack any part of the body such as the kidney, spine, and brain. Not everyone infected with TB bacteria becomes sick. *Mycobacterium tuberculosis* is a rod-shaped bacterium that is responsible for around 10 million new infections and 1.4 million deaths per year.[1]

Tuberculosis: Types

- Active TB Disease. Active TB is an illness in which the TB bacteria are rapidly multiplying and invading different organs of the body.
- Miliary TB. Miliary TB is a rare form of active disease that occurs when TB bacteria find their way into the bloodstream. Latent TB Infection.[2]

Symptoms

- Bad Cough for longer than three weeks either dry, yellow or green mucus and in some cases bloody mucus.
- Weight Loss.
- Fatigue.
- Shortness of Breath.
- Fever.
- Night Sweats.
- Lack of appetite.[3]

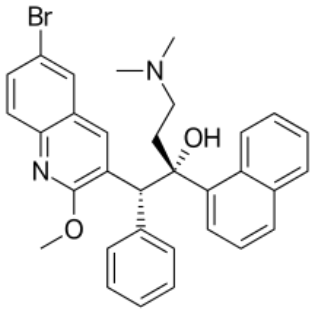

Figure-1: Structure of Bedaquiline.

Chemistry: Formula: $C_{32}H_{31}BrN_2O_2$, Molar mass: 555.516 g·mol^{-1}

Bedaquiline is a diarylquinoline antimycobacterial used in combination with other antibacterials to treat pulmonary multidrug resistant tuberculosis (MDR-TB).[4] Bedaquiline [CAS: 843663-66-1; IUPAC: (1R,2S)-1-(6-Bromo-2-methoxy-3-quinolyl)-4-dimethylamino-2-(1-naphthyl)-1-phenylbutan-2-ol], sold under the brand name Sirturo, is a medication used to treat active tuberculosis. Specifically, it is used to treat multi-drug-resistant tuberculosis (MDR-TB) along with other medications for tuberculosis. It is used by mouth. Bedaquiline is a member of the diarylquinoline class of drugs and has a unique mechanism of action, targeting the adenosine triphosphate (ATP) synthase enzyme of the TB mycobacteria.[5]

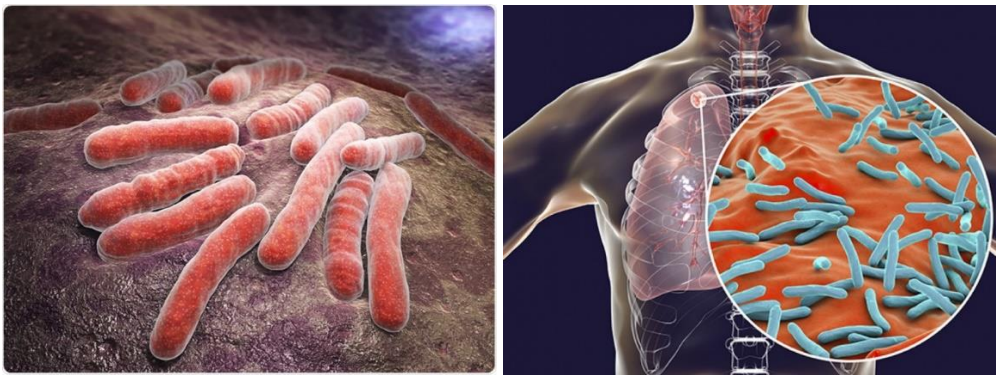

Figure-2: Tuberculosis bacteria.

Mode of action: ATP-synthase is used in the process by which *M. tb* generates its energy supply. Bedaquiline (Sirturo) is a diarylquinoline; its mechanism of action is adenosine triphosphate synthase inhibition. It has potent activity against *M. tuberculosis*. Common side effects include nausea, joint pains, headaches, and chest pain. Serious side effects include QT prolongation, liver dysfunction, and an increased risk of death. While harm during pregnancy has not been found, it has not been well studied in this population. It is in the diarylquinoline antimycobacterial class of medications. It works by blocking the ability of *M. tuberculosis* to make adenosine 5'-triphosphate (ATP). Bedaquiline is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *M. tuberculosis.*[6]

Bedaquiline blocks the proton pump for ATP synthase of mycobacteria. It is the first member of a new class of drugs called the diarylquinolines. Bedaquiline is bactericidal. ATP production is required for cellular energy production and its loss leads inhibition of mycobacterial growth within hours of the addition of bedaquiline. The onset of bedaquiline-induced mycobacterial cell death does not occur until several days after treatment, but nonetheless kills consistently thereafter. 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. Bedaquiline is a bactericidal antimycobacterial drug belonging to the class of diarylquinoline. The quinolinic central heterocyclic nucleus with alcohol and amine side chains is responsible for bedaquiline-mediated antimycobacterial activity. Although it is closely related to fluoroquinolones, bedaquiline does not affect DNA gyrase; instead, bedaquiline inhibits the c subunit of ATP synthase responsible for synthesizing ATP. Consequently, bedaquiline can be used to treat mycobacterial infection, particularly tuberculosis (TB). Although the current standard of TB treatment of anti-TB drugs for 2 months, including 2 key drugs isoniazid and rifampin, is highly effective, the emergence of multidrug-resistant TB (MDR-TB) to isoniazid and rifampin has substantially worsened patient's outcome. Bedaquiline was approved by the FDA on December 28, 2012, to treat pulmonary MDR-TB, following favorable results in multiple pre-clinical and clinical studies. It is the first drug that was approved in the last 40 years by the FDA for TB unresponsive to current treatments on the market. Currently, bedaquiline is the last-line anti-TB drug and must only be used in an appropriate combination regimen.[7]

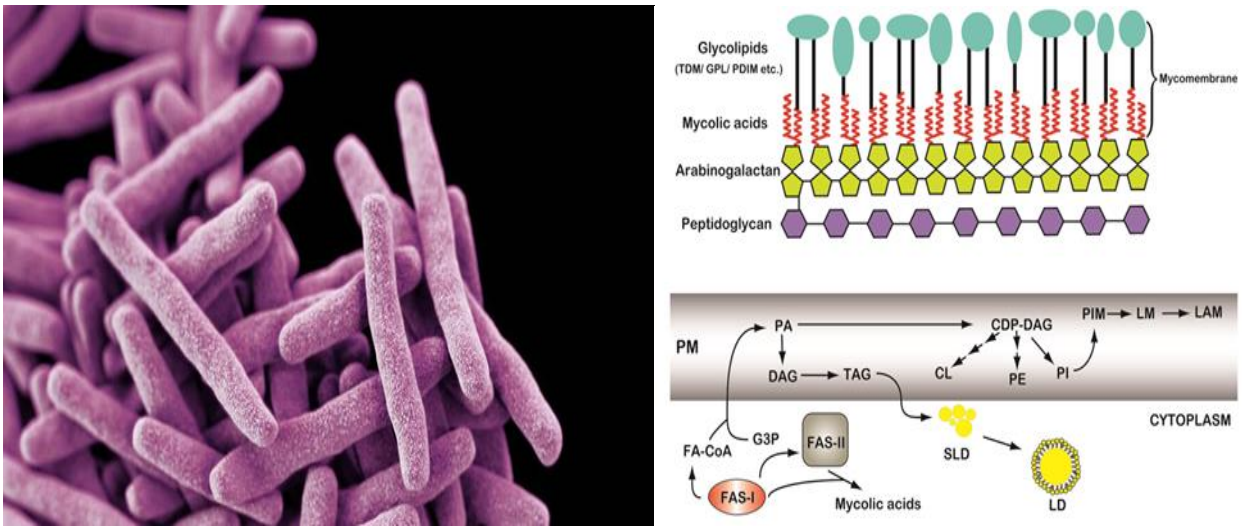

Figure-3: Bacillus and Mycolic acid.

Pharmacodynamics: Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (4-fold to 6-fold lower) than the parent compound. However, M2 plasma concentrations appeared to correlate with QT prolongation. Bedaquiline inhibits mycobacterial TB at a minimal inhibitory concentration (MIC) from 0.002-0.06 µg/ml and with a MIC50 of 0.03µg/ml. The proportion of naturally resistant bacteria is low, estimated to be in one strain over 107/108 bacteria. Bacteria that have smaller ATP stores (such as dormant, nonreplicating bacilli) are more susceptible to bedaquiline.[8]

Absorption: After the recommended dosing regimen of bedaquiline (400 mg for 2 weeks followed by 200 mg three times per week for 22 weeks), the Cmax and AUC24h were calculated to be 1.659 µg/ml and 25.863 µg.h/ml respectively. After a single oral dose administration of bedaquiline, maximum plasma concentrations (Cmax) are typically achieved at approximately 5 hours post-dose. Cmax and the area under the plasma concentration-time curve (AUC) increased proportionally up to 700 mg (1.75 times the 400 mg loading dose).

Administration of bedaquiline with a standard meal containing approximately 22 grams of fat (558 total Kcal) increased the relative bioavailability by approximately 2-fold compared to administration under fasted conditions. Bedaquiline should be taken with food to enhance its oral bioavailability.[9]

Volume of distribution: The volume of distribution in the central compartment is estimated to be approximately 164 Liters.

Protein binding: The plasma protein binding of bedaquiline is greater than 99.9%.

Metabolism: CYP3A4 was the major CYP isoenzyme involved in the in vitro metabolism of bedaquiline and the formation of the N-monodesmethyl metabolite (M2). Additionally, bedaquiline is also effective against nontuberculous mycobacteria, with MICs ranging from 0.06 to 0.5µg/ml. A potential for the development of resistance to bedaquiline in M. tuberculosis exists. Modification of the atpE target gene, and/or upregulation of the MmpS5-MmpL5 efflux pump (Rv0678 mutations) have been associated with increased bedaquiline MIC values in isolates of M. tuberculosis. Target-based mutations generated in preclinical studies lead to 8- to 133-fold increases in bedaquiline MIC, resulting in MICs ranging from 0.25 to 4 micrograms per mL. Efflux-based mutations have been seen in preclinical and clinical isolates. These lead to 2- to 8-fold increases in bedaquiline MICs, resulting in bedaquiline MICs ranging from 0.25 to 0.5 micrograms per mL.[10]

Route of elimination: After reaching Cmax, bedaquiline concentrations decline tri-exponentially. Based on preclinical studies, bedaquiline is mainly excreted in feces. The urinary excretion of unchanged bedaquiline was less than or equal to 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant.

Half-life: The mean terminal elimination half-life of bedaquiline and the N-monodesmethyl metabolite (M2) is approximately 5.5 months. This long terminal elimination phase likely reflects the slow release of bedaquiline and M2 from peripheral tissues.[11]

Clearance: Bedaquiline has a low apparent clearance of approximately 2.78 L/h.

Toxicity: There is no experience with the treatment of acute overdose with SIRTURO. Take general measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) in case of deliberate or accidental overdose. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Since bedaquiline is highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma. Bedaquiline was not carcinogenic in rats up to the maximum tolerated dose of 10 mg/kg/day. Exposures at this dose in rats (AUCs) were within 1-fold to 2-fold of those observed in adult patients in the clinical trials.[12]

No mutagenic or clastogenic effects were detected in the in vitro non-mammalian reverse mutation (Ames) test, in vitro mammalian (mouse lymphoma) forward mutation assay, and an in vivo mouse bone marrow micronucleus assay.
SIRTURO did not affect fertility when evaluated in male and female rats at approximately twice the clinical exposure based on AUC comparisons. There was no effect of maternal treatment on sexual maturation, mating performance, or fertility in the F1 generation exposed to bedaquiline in utero at approximately twice the human exposure.[13]

Food Interactions: Avoid alcohol. Take with food. Food significantly increases the oral bioavailability.

Table-1: Physicochemical parameters.

State	Solid	logP	6.37, 7.13
Water Solubility	0.999193 mg/mL	logS	-6.5
pKa	13.61 [acidic]	pKa	8.91 [basic]
Physiological charge	1	Hydrogen Acceptor	4
Hydrogen Donor	1	Rotable Bond Count	8
Polar Surface Area	45.59 $Å^2$	Refractivity	154.02 $m^3 \cdot mol^{-1}$
Polarizability	57.29 $Å^3$	Number of Rings	5
Lipinski Rule	No		

It is a small bacillus that can withstand weak disinfectants and can survive in a dry state for weeks. Its unusual cell wall is rich in lipids such as mycolic acid and cord factor glycolipid, is likely responsible for its resistance to desiccation and is a key virulence factor.

Figure-4: Formulation.

Conclusion: Bedaquiline fumarate (SirturoTM) 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 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. 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 timesper 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 Counselling

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.

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.

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