FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)

Megan Ruffner
Ohio Northern University

Kent Wilin
Ohio Northern University

Charles Hay
Ohio Northern University

Zachary Crawford
Ohio Northern University

Andrew Roecker
Ohio Northern University, a-rocker@onu.edu

Follow this and additional works at: https://digitalcommons.onu.edu/paw_review

Part of the Bacterial Infections and Mycoses Commons, Infectious Disease Commons, Medical Pharmacology Commons, and the Pharmaceutics and Drug Design Commons

Recommended Citation
Infectious Disease

FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)

Megan Ruffner, fifth-year pharmacy student from Defiance, Ohio; Kent Wilin, fourth-year pharmacy student from Findlay, Ohio; Charles Hay, fourth-year pharmacy student from Celina, Ohio; Zachary Crawford, fifth-year pharmacy student from Centerville, Ohio; Andrew Roecker, PharmD ’00, BCPS, professor of pharmacy practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-13-176-H01-P

Objectives
After completion of this program, the reader should be able to:
1. Describe the pathophysiology of tuberculosis.
2. Evaluate the need for new drug therapies in the treatment of multidrug-resistant tuberculosis.
3. Explain the mechanism of action of bedaquiline.
4. List the major side effects of bedaquiline.
5. Discuss how bedaquiline will positively impact current therapy.

Abstract
Tuberculosis (TB), caused by the acid-fast bacilli (AFB) Mycobacterium tuberculosis, is an infectious disease that continues to greatly impact morbidity and mortality worldwide; in 2011 it caused 1.4 million deaths. Some strains of the bacteria have become resistant to current treatment regimens, resulting in multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. The emergence of these resistant strains of bacteria calls for new treatment regimens that can quickly and effectively eradicate the organism. The U.S. Food and Drug Administration (FDA) recently approved Sirturo® (bedaquiline) with the indication of MDR pulmonary TB. Bedaquiline introduces a novel mechanism of action via the inhibition of bacterial adenosine triphosphate (ATP) synthase. In this article we will further explore the background information for TB, current treatment regimens, adverse effects of bedaquiline and studies that explore the place for bedaquiline in the treatment of TB.

Introduction
Tuberculosis, caused by Mycobacterium tuberculosis, remains a prevalent disease globally with approximately one third of the world’s population infected. According to the Centers for Disease Control and Prevention (CDC), 10,528 cases of TB were reported in the United States in 2011, which is a 5.8 percent decrease from the number of cases reported in 2010. However, the World Health Organization (WHO) estimates that in 2011 there were 8.7 million new cases and 1.4 million deaths from TB worldwide. Tuberculosis is a major consideration for human immunodeficiency virus (HIV) infected patients, being the leading killer of this population. This shows that while TB is on the decline in the United States, the vast impact on worldwide incidence and mortality remains a concern.

Mycobacterium tuberculosis is transmitted via inhalation of droplets in the air and typically infects the lungs when active. Tuberculosis can be latent or active in an individual. Latent TB occurs when a healthy individual inhales the organism, the lungs allow the organism to enter the body via macrophages and the lymphatic system, but the body does not allow the bacteria to actively grow. Patients with latent TB will not feel ill or be contagious; however, a latent infection may become active if an individual’s immune system becomes compromised. Active TB presents with symptoms such as severe cough, chest pain, hemoptysis, fatigue and fever. Individuals that are immunocompromised, such as those with HIV infection, are at increased risk of developing the active infection.

A Mantoux tuberculin skin test may identify, but not differentiate, both latent and active TB; a chest x-ray and AFB smear can confirm an active infection. Tuberculosis is an AFB, rendering it impossible to identify via gram stain, and requiring identification via special AFB smears. Culturing of a sputum sample must be done to test the specimen for susceptibility to drug regimens.

To avoid producing resistant strains of TB and to ensure complete eradication of the organism, it is recommended to use multiple agents when treating active TB. Despite such precautions, MDR TB and XDR TB continue to present an obstacle in treatment. MDR TB is defined as being resistant to the drugs isoniazid and rifampin; this presents an obstacle to treatment because these are two drugs commonly used to treat TB. Extensively drug-resistant TB is resistant to these two drugs as well as any fluoroquinolone and any of the injectable second-line drugs for TB, such as amikacin or kanamycin. Research and development of new drugs to treat TB are needed for multiple reasons including shortening the duration of treatment regimens and improving treatment of MDR and XDR TB.

Current Treatment
The American Thoracic Society, CDC, and the Infectious Diseases Society of America (IDSA) have partnered to publish treatment guidelines for TB in the United States. For drug susceptible strains of TB, an initial treatment regimen of ethambutol (EMB), isoniazid (INH), rifampin (RIF), and pyrazinamide (PZD) for two months is recommended followed by a maintenance treatment of six to nine months using various combinations of the same drugs. If drug resistant forms of TB develop during treatment, at least two or three new drugs should be added to the regimen in replacement of...
FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)

### Table 1. Options for Initial Phase of Drug Susceptible Tuberculosis.6

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Frequency and Duration</th>
<th>Options for Continuation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>7 days/week for 8 weeks or 5 days/week for 8 weeks</td>
<td>1,2,3</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>7 days/week for 2 weeks then twice weekly for 6 weeks or 5 days/week for 2 weeks then twice weekly for 6 weeks</td>
<td>2,3</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>3 times weekly for 8 weeks</td>
<td>4</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>7 days/week for 8 weeks or 5 days/week for 8 weeks</td>
<td>5</td>
</tr>
</tbody>
</table>

*Referenced in Table 2

### Table 2. Options for Continuation Phase of Drug Susceptible Tuberculosis.6

<table>
<thead>
<tr>
<th>Option #</th>
<th>Drug Combination</th>
<th>Frequency and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH/RIF</td>
<td>7 days/week for 18 weeks or 5 days/week for 18 weeks</td>
</tr>
<tr>
<td>2</td>
<td>INH/RIF</td>
<td>Twice weekly for 18 weeks</td>
</tr>
<tr>
<td>3</td>
<td>INH/RPT*</td>
<td>Once weekly for 18 weeks</td>
</tr>
<tr>
<td>4</td>
<td>INH/RIF</td>
<td>Three times weekly for 18 weeks</td>
</tr>
<tr>
<td>5</td>
<td>INH/RIF</td>
<td>7 days/week for 31 weeks or 5 days/week for 31 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly for 31 weeks</td>
</tr>
</tbody>
</table>

*RPT (rifapentine)

The agents to which resistance has been acquired. These drugs should be selected based upon susceptibility testing and may include drugs such as streptomycin, amikacin, kanamycin, p-aminosalicylic acid, or a fluoroquinolone.

The current treatment regimen, as described above, presents multiple obstacles to optimal treatment of TB.1 The high pill burden along with the duration of treatment of at least six months leads to patient noncompliance. Direct observation therapy has been implemented to avoid this issue, but is expensive and time-consuming. The current first-line treatment regimen presents many potentially severe side effects, such as hepatotoxicity and permanent visual impairment.8 Rifampin decreases the concentrations of protease inhibitors, which are a class of drugs used to treat HIV infection; the common presence of HIV and TB as comorbidities presents a treatment dilemma. These are a few of the foremost reasons why new drugs for TB are desperately needed. The potential impact of bedaquiline on TB treatment and these treatment obstacles will be explored throughout the remainder of the article.

### Development

Bedaquiline (Sirturo®) was approved on December 28, 2012, by the FDA for MDR pulmonary tuberculosis after going through the FDA’s priority review and has received orphan-product designation.9 Fast tracking this medication has made it available to patients sooner but comes with less substantial data than is usually seen with a newly marketed drug. The accelerated approval of bedaquiline allowed it to be placed on the market with data that show it is reasonably likely to provide clinical benefits to patients. Janssen Therapeutics (the manufacturer of bedaquiline) will continue to conduct studies to confirm the drug’s effectiveness and safety.

### Mechanism of Action

Bedaquiline is of the diarylquinoline class of drugs and has been seen to act through inhibition of bacterial ATP synthase by inhibiting the c subunit of the enzyme.10 Bedaquiline contains two chiral centers giving the molecule several possible stereoisomers, of which the (R,S) configuration has been seen to be the most active against TB. This stereoselectivity is indicative of specific binding to a target protein. Through gel electrophoresis of two eluted proteins from an affinity column, the ATP subunits were identified as the target. Further testing with a Biacore carboxymethyl-Sepharose chip identified ATP synthase subunit c as the primary target for bedaquiline. Current treatments target cell wall synthesis, ribonucleic acid (RNA) transcription, and pH levels of the environment (isoniazid and ethambutol, rifampin, and pyrazinamide respectively). The novel method of targeting ATP synthase with bedaquiline allows for use against resistant TB
and latent TB by depleting the bacterium’s energy supplies. An extensive target study by Haagsma et al. has confirmed the action of bedaquiline takes place at the c subunit of ATP synthase, specifically at the interface between subunits a and c to block conformational changes in ATP synthase. The study also shows that bedaquiline does not compete with protons for a common binding site and, thus, is not affected by proton motor force like such drugs as sodium azide and other ATP synthase inhibitors which increases the efficacy of bedaquiline. Bedaquiline, however, is dependent upon electrostatic attractive forces that bind subunit c. It was seen that as sodium chloride concentrations increased in the body, bedaquiline binding affinity decreased. It is also noteworthy to include that bedaquiline’s activity is not affected significantly by pH changes in the range from 5.25 to 7.5. This is advantageous due to the acidic environment of the lung where latent TB can often be found but is extremely difficult to treat.

**Unique Features**

Bedaquiline has shown to be a viable drug for targeting latent mycobacteria. Its novel mechanism of action provides another option for treatment in MDR TB, which by definition is resistant to the more familiar mechanisms of action. Researchers found that dormant mycobacteria have active and functional ATP synthase. Depleting ATP in the dormant bacteria by bedaquiline mediated inhibition of ATP synthase leads to bactericidal activity. Researchers also found that bedaquiline was slightly more effective in dormant bacilli compared to replicating bacilli, while the present first and second-line TB antibiotics exhibited strong bactericidal activity on replicating mycobacteria but not on the dormant bacilli. This unique feature of bedaquiline could reduce the time needed to treat infection when used in combination with current first and second-line therapies. Bedaquiline was seen to be effective at a dose of 400 mg at days 4 through 7 in an early bactericidal activity study by Rustomjee. This study suggests that bedaquiline could be used as a sterilizing agent in current TB regimens because of the drug’s ability to deplete mycobacterium energy stores.

**Adverse Effects**

When used in the appropriate situation, bedaquiline offers health care providers and patients with another weapon against MDR TB; however, it is important to note that use of bedaquiline has been associated with serious adverse events that warrant attention and monitoring. The FDA has placed two black box warnings on bedaquiline. The first warns that patients may experience QT prolongation. The concern with QT prolongation is the increased risk of the development of arrhythmias, especially torsade de pointes. Torsade de pointes is a ventricular arrhythmia that is life threatening and has specifically been linked to QT prolongation. Other risk factors that increase the risk of adverse outcomes from QT prolongation include uncompensated heart failure, low serum electrolyte levels and hypothyroidism. Because of bedaquiline’s possible effect on QT prolongation, it is recommended that an electrocardiogram be recorded at the beginning of therapy and at weeks 2, 12, and 24. If an arrhythmia develops, therapy should be discontinued. Additionally, baseline liver enzymes and serum electrolyte levels should be recorded in case there is a need for compensation during therapy. The second FDA black box warning alerts health care providers that in trials bedaquiline was associated with a higher risk of death compared to placebo. In one of the clinical trials that led to bedaquiline’s approval, the number of deaths in the treatment group was statistically significantly higher than the placebo group; however, all of the placebo deaths and roughly half of the bedaquiline deaths seemed to be related to tuberculosis. The black box warning instructs health care providers to only use bedaquiline “if no other effective treatment regimen is available.” This black box warning truly demonstrates why bedaquiline is reserved for those patients who have no other options. The early approval of a drug with such a warning demonstrates the urgent need for effective treatment of MDR TB. Janssen will be distributing educational material with the medication to ensure the drug is used appropriately.

**The most common patient-reported side effects are nausea, painful or stiff joints, headache, chest pain and hemoptysis.** These adverse events fall within the mild to moderate range, and only nausea has been reported statistically as significantly higher than placebo. As a major substrate for CYP3A4, bedaquiline should be administered with caution with drugs that induce or inhibit CYP3A4. Bedaquiline should also not be administered with alcohol, ivabradine, mifepristone, St John’s Wort or tocilizumab. Also, it is important that health care providers monitor patients’ liver function. If aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations last for longer than two weeks, it is advised that therapy should be stopped. Through animal studies, bedaquiline has been rated at pregnancy risk factor B.

**Literature Review**

**The diaryquinoline TMC207 for multidrug-resistant tuberculosis.**

As part of the phase 2 trials for bedaquiline, Diacon et al. performed a double-blind, randomized placebo-controlled study in South Africa. Eligible study participants had confirmed MDR TB and received either placebo (24 patients) or bedaquiline 400 mg (23 patients) once daily for weeks 1 and 2, followed by 200 mg three times a week for weeks 3 through 8 along with a preferred background regimen of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone (modifications could be made following susceptibility testing or adverse events). After the eight weeks of study medication, participants continued the background medication regimen only and were followed for a total of two years. Administration of each dose of study medication was supervised to ensure compliance. The authors reported results after eight weeks and also at two years. Outcomes were measured via sputum samples cultured in a liquid broth medium (MGIT system) before treatment initiation and weekly thereafter during study medication administration. Quantitative sputum colony counting was also performed. Blood samples were monitored for plasma levels of bedaquiline.

In the literature published at eight weeks, the authors con-
FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)

### Infectious Disease

Table 3. Common Adverse Effects of Conventional TB Therapy Compared To Bedaquiline.9,10-21

<table>
<thead>
<tr>
<th></th>
<th>Ethambutol</th>
<th>Isoniazid</th>
<th>Rifampin</th>
<th>Pyrazinamide</th>
<th>Bedaquiline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Myocarditis</td>
<td>Hypertension, tachycardia</td>
<td>Edema, flushing</td>
<td>X</td>
<td>Chest pain, Black box warning for QT prolongation</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>Confusion, hallucinations, headache</td>
<td>Depression, fatigue, fever, headache</td>
<td>Ataxia, headache</td>
<td>Fatigue</td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Acute gout</td>
<td>Gynecomastia, hyperglycemia, metabolic acidosis</td>
<td>Adrenal insufficiency</td>
<td>Gout (rare)</td>
<td>X</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Anorexia, nausea/vomiting</td>
<td>Anorexia, nausea/vomiting</td>
<td>Gl upset</td>
<td>Anorexia, nausea/vomiting</td>
<td>Anorexia, nausea/vomiting</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td>Anemia, leukopenia, thrombocytopenia</td>
<td>Agranulocytosis, anemia</td>
<td>Agranulocytosis, anemia, leukopenia, thrombocytopenia</td>
<td>Thrombocytopenia (rare)</td>
<td>X</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>Elevated liver enzymes and toxicity</td>
<td>Black box warning for hepatitis</td>
<td>Increase liver enzymes (rare hepatitis)</td>
<td>Dose related hepatotoxicity (rare) Fever</td>
<td>Increase liver enzymes</td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
<td>Peripheral neuropathy</td>
<td>Dose related peripheral neuropathy</td>
<td>General numbness</td>
<td>Myalgia</td>
<td>Arthralgia</td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
<td>Impairment of color vision (inflammation of optic nerve)</td>
<td>Blurred vision</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Nephritis</td>
<td>X</td>
<td>Elevations in BUN and uric acid leading to potential renal failure</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Pneumonitis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Hemoptyis</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>X</td>
<td>Lupus-like syndrome</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Included that taking bedaquiline resulted in crucial time-dependent bactericidal activity. The bedaquiline group had quicker conversions to a negative sputum culture (hazard ratio 11.8, 95 percent confidence interval: 2.3 to 61.3). In the eight weeks, 48 percent of the treatment group converted to a negative culture, while 9 percent of the treatment group did. Log10 colony forming units (CFU) declined more rapidly in the treatment group. At eight weeks, and also at two years, nausea was the only side effect that appeared significantly more in the treatment group than the placebo group. In the two year follow-up article, the authors noted that 50 percent culture conversion for the treatment group occurred at 78 days, while this occurred at 129 days in the placebo group; this again demonstrates the advantageous time-dependent activity of bedaquiline. After two years, it was also seen that more patients receiving placebo (4/18) than treatment (0/16) that were initially susceptible to ofloxacin developed resistance to it; suggesting bedaquiline lowers the risk of acquiring additional drug resistance throughout therapy.

This study shows that bedaquiline may be an important drug for reducing time for treating MDR TB and may potentially...

May 2013 Volume 4, Issue 2 THE PHARMACY AND WELLNESS REVIEW 35
Infectious Disease

FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)

decrease the incidence of newly formed resistance during treatment. Although the study was well designed, the small sample size (47 patients) is a limitation to the external validity of the study. Due to this, larger trials investigating more safety aspects of the drug are needed to determine the future place for this new drug in the TB guidelines.

**14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomized trial.**

Diacon et al. performed a phase 2A, partially double-blinded, randomized trial to assess early bactericidal activity (EBA), safety, tolerability, and pharmacokinetics of various combinations of various TB drugs (Table 4). This study was designed recognizing the need for shorter and better tolerated regimens needed to treat TB worldwide.

Patients were from two outpatient clinics in South Africa and included if they were otherwise relatively healthy and had confirmed fully drug susceptible TB. Bedaquiline and PA-824, a nitroimidazo-oxazine in the pipeline, were the new agents included in the study and were chosen based upon their synergism with pyrazinamide in murine experiments. Rifafour e-275 was used as the control in the study, representing current standard treatment. Rifafour e-275 contains isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg; patients received two (30-37 kg), three (38-54 kg), or four (55-70 kg) a day based on body weight. Experimental group dosing is described in Table 4. Fifteen patients were included in each study group and 10 patients were included in the control group.

The primary outcome of the study was the 14 day early bactericidal activity (EBA) of each combination based upon the daily fall in CFU per mL of sputum measured via log_{10} CFU; sputum samples were collected daily overnight. Safety monitoring included daily vital signs and physical examination as well as 12-lead electrocardiogram (ECG) on days 1, 3, 8, and 14. After the two weeks, patients were referred to local TB clinics for a standard course of therapy and returned for study follow-up visits at 14, 28, and 90 days after study completion. The study was not powered to compare differences between treatment groups and the control.

The results showed that the mean 14 day EBA of PA-824, moxifloxacin, and pyrazinamide was 0.233 [SD 0.128], which was higher than any other group. The other groups were bedaquiline at 0.061 [0.069]; bedaquiline and pyrazinamide at 0.131 [0.102]; bedaquiline and PA-824 at 0.114 [0.050]; PA-824 and pyrazinamide at 0.154 [0.040], and rifafour e-275 at 0.140 [0.094].

The authors conclude that bedaquiline/PA-824 and PA-824/pyrazinamide/moxifloxacin showed activity comparable with that of current standard treatment and thus may be studied further as building blocks of future front line regimens. There is currently a trial sponsored by the Global Alliance for TB Drug Development exploring the combination of bedaquiline, PA-824, clofazimine, and pyrazinamide for EBA activity.

**Safety, tolerability, and pharmacokinetic interactions of the antituberculosis agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS clinical trials group study A5267.**

In April 2012, Dooley et al. published a study in the Journal of Acquired Immune Deficiency Syndrome that examined the pharmacokinetic related interaction of bedaquiline therapy alone, as well as in conjunction with the HIV medication efavirenz. The rationale behind this study was that roughly 15 percent of patients infected with TB also suffer from HIV. This study is important because it also investigates the pharmacokinetic properties of bedaquiline monotherapy.

Conducted in the United States, this phase 1 trial consisted of healthy individuals 18 to 65 years in age. Notable exclusion criteria included positive HIV antibody test, elevated hepatic enzymes, below average hemoglobin, white cell count, or platelets, irregular ECG, estimated creatinine clearance below 50 ml/min, or any indication of possible TB infection. Additionally, “women of reproductive potential” and current users of a prescription drug known to inhibit CYP3A were excluded. To begin the study, participants were given a single 400 mg dose of bedaquiline. Plasma levels of bedaquiline and

---

**Table 4. Treatment Group Regimen Description.**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Bedaquiline</th>
<th>Pyrazinamide</th>
<th>PA-824</th>
<th>Pyrazinamide</th>
<th>Moxifloxacin</th>
<th>Rifafour e-275</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1-700 mg</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2-500 mg</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

---

The Pharmacy and Wellness Review  May 2013 Volume 4, Issue 2
one of its metabolites (M2) were measured 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, 216, 264, and 336 hours after the dose. This was designated period 1. Over the next 14 days, participants received 600 mg of efavirenz nightly. On day 28 of the trial (day 14 of efavirenz therapy) the participant’s efavirenz plasma levels were drawn 1, 2, 3, 4, 8, 12, and 24 hours postdose. The following day, 400 mg of bedaquiline was again administered to participants in addition to the continuation of 600 mg efavirenz nightly. Plasma bedaquiline/M2 levels were collected per the same schedule as period 1.

At the end of the study the researchers compared the area under the curve (AUC), maximum concentration (Cmax), time to maximum concentration (Tmax), and half-life (t1/2) of bedaquiline and M2 as a monotherapy and compared these values to the ones taken when efavirenz was administered concomitantly. Of statistical relevance, efavirenz was found to decrease the AUC of bedaquiline by about 20 percent. It is important to note though, that the participants’ bedaquiline levels were still therapeutic. Additionally, it increased the Cmax of M2; however, the AUC of M2 was unchanged. This correlates to an increased clearance of M2 in the presence of efavirenz. While this study addressed a key consideration in the treatment of MDR TB, it is only a beginning. Dooley et al. achieved a power above 80 percent. While this is commendable, they still only used a small sample size of healthy volunteers. A much larger study needs to be conducted that targets a population similar to the patients for whom bedaquiline is intended. 

Conclusion

Worldwide, tuberculosis is the second highest cause of death from an infectious disease.17 Of those patients who are currently infected with tuberculosis, 35.3 percent of the newly diagnosed patients have a MDR strain, while 76.5 percent of previously treated patients have a MDR strain. These statistics alone demonstrate the importance of bedaquiline and other new TB drugs. While bedaquiline is currently only approved for MDR TB, some early studies show potential for this drug to be included in the early phase of future treatment regimens to reduce the total time of treatment; this in turn would have a positive impact on patient compliance. Also, it appears as if bedaquiline could be important in the treatment of patients with both TB and HIV; this is shown by the small impact of efavirenz on bedaquiline levels as noted above in the literature review. Though there are serious adverse events associated with bedaquiline therapy, health care professionals must weigh these risks against the fact that there are not many options for patients with MDR TB. When used appropriately, bedaquiline can offer some help to patients suffering from this tenacious disease.

References

Assessment Questions

1. Tuberculosis (TB) is an important consideration for patients with __________ since it is the leading cause of mortality in this population.
   A. Diabetes mellitus
   B. HIV
   C. Hypertension
   D. Sleep apnea

2. TB most commonly infects which part of the body?
   A. Heart
   B. Liver
   C. Skin and soft tissue
   D. Lungs

3. Multidrug-resistant (MDR) TB is defined as:
   A. TB that no longer responds to any medications
   B. TB that is resistant to a fluoroquinolone
   C. TB that is resistant to isoniazid and rifampin
   D. TB that responds well to first-line treatment options

4. Which of the following is NOT a reason for using multiple medications in a regimen for treating active TB?
   A. To avoid resistance development
   B. To ensure complete eradication of the organism
   C. To attack the organism with multiple mechanisms of action
   D. To make sure the dose of one particular medication is not too high for tolerance of side effects

5. Which of the following is a potential benefit of including bedaquiline in an MDR TB regimen?
   A. Reducing total time of treatment
   B. Allowing a single medication to be used for the treatment of active TB
   C. Availability in a wide variety of dosage forms
   D. None of the above are benefits of bedaquiline treatment

6. What is the primary target for bedaquiline?
   A. Cell wall synthesis
   B. ATP synthase
   C. RNA transcription
   D. pH levels

7. Bedaquiline is affected by which of the following?
   A. Electrostatic attractive forces
   B. Proton motor force
   C. pH from 5.25 – 7.5
   D. All the above

8. Bedaquiline has shown to be a viable drug for targeting latent mycobacteria.
   A. True
   B. False

9. Bedaquiline contains a black box warning for which side effect?
   A. Hepatotoxicity
   B. Gastrointestinal bleeding
   C. QT prolongation
   D. None of the above

10. Prior to bedaquiline therapy, which patient-specific baseline levels should be measured?
    A. Liver enzymes
    B. ECG
    C. Serum electrolytes
    D. All of the above

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 05/16/16.
To receive continuing education credit for this program, visit [www.onu.edu/pharmacy/CE](http://www.onu.edu/pharmacy/CE) OR fill out the form below including your indicated answers to the assessment questions and return to:

**Office of Continuing Education at the Raabe College of Pharmacy**  
Ohio Northern University  
525 South Main Street  
Ada, Ohio 45810

Ohio Northern University Continuing Education Registration & Evaluation Form  
Raabe College of Pharmacy Continuing Education Evaluation Form

**Program Title:** FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)  
UAN: 0048-0000-13-176-H01-P  CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

Name:  
Address:  
City: State: Zip:  
Phone: Email:  
Pharmacy License #: State: ONU Alumni? Y N

<table>
<thead>
<tr>
<th>Program Content:</th>
<th>Strongly Disagree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The program objectives were clear.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>The program met the stated goals and objectives:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describe the pathophysiology of tuberculosis.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Evaluate the need for new drug therapies in the treatment of multidrug-resistant tuberculosis.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Explain the mechanism of action of bedaquiline.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>List the major side effects of bedaquiline.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Discuss how bedaquiline will positively impact current therapy.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>The program met your educational needs.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Content of the program was interesting.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Material presented was relevant to my practice.</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Comments/Suggestions for future programs:**

---

Thank you!

**Answers to Assessment Questions—Please Circle Your Answer**

1. A B C D  
2. A B C D  
3. A B C D  
4. A B C D  
5. A B C D  
6. A B C D  
7. A B C D  
8. A B  
9. A B C D  
10. A B C D

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 05/16/16.