APPLICATION NUMBER:

212862Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type                  NDA
Application Number                212862
PDUFA Goal Date                  August 14, 2019
OSE RCM #                       2018-2701 and 2018-2705

Reviewer Name(s)                  Mei-Yean Chen, Pharm.D.
Team Leader                      Elizabeth Everhart, RN, MSN, ACNP
Division Director                Cynthia, LaCivita, Pharm.D.
Review Completion Date           July 8, 2019
Subject                          Evaluation of Need for a REMS

Established Name                  Pretomanid
Trade Name                       Pretomanid (Applicant intends to use the established name)
Name of Applicant                Global Alliance for TB Drug Development Inc. (TB Alliance)
Therapeutic Class                An anti-tuberculosis agent
Formulation(s)                   200 mg tablet
Dosing Regimen                   200 mg orally once daily for 26 weeks, in combination with bedaquiline and linezolid
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Pretomanid is necessary to ensure the benefits outweigh its risks. Global Alliance for TB Drug Development, Inc. (TB Alliance) submitted a New Drug Application (NDA) 212862 for pretomanid with the proposed indication, “as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Pretomanid is indicated for use in a limited and specific population.” If approved, the product will have Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) language as follows:

- Limited Population: Pretomanid is indicated as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of XDR, treatment-intolerant or nonresponsive MDR TB.
- Limitations of Use:
  - Pretomanid are not indicated in patients with
    - Drug-sensitive TB
    - Latent infection due to *Mycobacterium tuberculosis*
    - Extra-pulmonary infection due to *Mycobacterium tuberculosis*.
    - MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
  - Safety and Effectiveness of Pretomanid Tablets has not been established for its use in combination with drugs other than bedaquiline and linezolid at the recommended dosing regimen.

The applicant did not submit a proposed REMS or risk management plan with this application.

The most concerning adverse reaction associated with the use of pretomanid is hepatotoxicity. In a multicenter, open-label study (Study 1) conducted in patients with XDR, or treatment intolerant/nonresponsive (TI/NR) MDR pulmonary TB, 27.5% of patients experienced an increase in transaminases and 2 patients met potential Hy’s law criteria. There were no patients withdrawn from the study because of hepatotoxicity, and no death was considered related to drug-induced hepatotoxicity. The labeling will advise Healthcare Providers (HCPs) to monitor for signs and symptoms of potential liver toxicity. The other risks associated with the pretomanid-bedaquiline-linezolid regimen include myelosuppression, peripheral and optic neuropathy, QT prolongation, reproduction effects in male rats, and lactic acidosis. The labeling will communicate these risks in the Warnings and Precautions section. DRISK and DAIP agree that a REMS is not needed to ensure the benefits of pretomanid outweigh its risks.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pretomanid is necessary to ensure the benefits outweigh its risks. TB Alliance submitted a NDA 212862 for pretomanid with the proposed indication, as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with XDR or treatment-intolerant or non-responsive MDR TB. Pretomanid is indicated for use in a limited and specific population. If approved, the prescribing information will include LPAD language as follows:
- Limited Population: Pretomanid is indicated as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of XDR, treatment-intolerant or nonresponsive MDR TB.
- Limitations of Use:
  - Pretomanid are not indicated in patients with
    - Drug-sensitive TB
    - Latent infection due to *Mycobacterium tuberculosis*
    - Extra-pulmonary infection due to *Mycobacterium tuberculosis*.
    - MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
  - Safety and Effectiveness of Pretomanid Tablets has not been established for its use in combination with drugs other than bedaquiline and linezolid at the recommended dosing regimen.

This application is under review in the Division of Anti-Infection Products (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

### 2.1 PRODUCT INFORMATION

Pretomanid, an NME,\(^a\) is a member of a class of compounds known as nitroimidazooxazine. During early development, pretomanid was referred to as PA-824. TB Alliance submitted a NDA 212862 for pretomanid with the proposed indication, as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with XDR or treatment-intolerant or nonresponsive MDR TB.

Pretomanid has demonstrated in vitro activity against *Mycobacterium tuberculosis* (*M. tuberculosis*). Pretomanid has also demonstrated anti-*M. tuberculosis* activity in combination with bedaquiline and linezolid, in animal models and in human trials. In murine tuberculosis models, the combination of pretomanid, bedaquiline and linezolid reduced bacterial counts in the lungs to a greater extent and resulted in fewer relapse at 2-3 month post-therapy compared to 2-drug combinations.

Pretomanid kills actively replicating *Mycobacterium tuberculosis*, by inhibiting mycolic acid biosynthesis thereby blocking cell wall production. Under anaerobic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release.\(^1\)

The recommended dosage of pretomanid is 200 mg orally once daily for 26 weeks. Pretomanid should be administered with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week orally for a total of 26 weeks) and linezolid (1200 mg daily orally for up to 26 weeks, with dose adjustments for known linezolid toxicities). Pretomanid is not currently approved in any jurisdiction.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212862 relevant to this review:

\(^a\) Section 505 -1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Tuberculosis (TB) is an infectious disease caused by the bacterium *M. tuberculosis*, which is spread by airborne transmission. One fourth of the world’s population is infected with TB. In 2017, 10 million people around the world became sick with TB disease. There were 1.3 million TB-related deaths worldwide. A total of 9,105 TB cases were reported in the United States (US) in 2017.² A person who becomes infected with the TB bacillus remains infected for years. Latent TB infection is a person with a healthy immune system does not become ill, but is not able to eliminate the infection without taking an anti-TB drug. About 10% of healthy persons who have latent TB infection will become ill with active TB at some time during their lives. When TB bacteria become active and immune system cannot stop the bacteria from growing, this will make a person sick. For patients who have drug-susceptible TB, the combination of first-line drugs (isoniazid [INH], rifampin [RIF], ethambutol [EMB], and pyrazinamide [PZA]) given as a 6-month standard regimen can achieve cure. Treatment failure is defined as continued positive sputum cultures during the therapy. After 3 months of multidrug treatment, 90-95% of patients will have negative cultures and show clinical improvement. Patients whose sputum cultures remain positive after 4 months of treatment should be considered as treatment failure. Possible reasons for treatment failure include nonadherence to the drug regimen, drug resistance, malabsorption of drugs, laboratory error, and extreme biological variation in response.

MDR TB is defined as TB that is resistant to at least INH and RIF.³ MDR TB usually requires 18-24 months of treatment with 4-6 drugs (first-line drugs plus an injectable agent, a fluoroquinolone, and other second-line drug as needed) that are less effective, more toxic, and more costly than a standard first-line therapy.⁴ The cure rate for patients with MDR TB decreases from 95% to less than than 60%. According to a report by Dean AS and Cox H in 2017,⁵ an estimated 3.9% of new TB cases and 21% of previously treated cases had MDR TB in 2016 globally.⁶ Per Center of Disease Control (CDC) TB factsheet,⁶ there

³ Section 505 -1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
were 8,982 cases of drug-susceptible TB and 121 MDR TB cases in the US in 2017. According to World Health Organization (WHO) global tuberculosis report 2015, approximately 480,000 individuals developed MDR TB each year globally.\(^7\)

XDR TB, first reported in 2006, is a rare type of MDR TB that is resistant to INH and RIF, plus any fluorquinolone and at least one of three injectable second-line drugs (i.e., kanamycin, amikacin, or capreomycins). Because XDR TB is resistant to the most potent TB drugs, patient are left with treatment options that are much less effective. Some TB control programs have shown that cure is around 30% to 50% of affected people.\(^8\) According to “The National Tuberculosis Surveillance System report 1993-2011”, there were 63 cases of XDR TB in the US between 1993-2011. Per CDC’s TB factsheet, there were 2 cases of XDR TB in the US in 2017.

TB cases are increasing, and the most serious aspect of the problem is the outbreaks of MDR TB, which is an urgent public health problem. MDR-TB has emerged in epidemic proportions in the wake of widespread Human Immunodeficiency Virus (HIV) infection in the world’s poorest population. According a report in 2010,\(^9\) a retrospective observation study in South Africa, from 2005 to 2007, 272 MDR TB and 382 XDR TB cases were diagnosed; HIV-coinfection rates were 90 and 98%, respectively. One-year mortality was 71% for MDR and 83% for XDR TB patients; 40% of MDR and 51% of XDR TB cases dies within 30 days of sputum collection.\(^c\)

### 3.2 Description of Current Treatment Options

Current treatment regimens for XDR-TB or treatment intolerant or non-responsive MDR-TB include a combination of 5 or more second and third line oral drugs with an injectable drug. The regimen is not defined, but is tailored based on the susceptibility pattern of the \textit{M. tuberculosis} isolate. Patients are treated up to 18 months or longer. The regimen is very expensive, takes a long time to complete, and has potentially life-threatening side effects. Serious side effects, such as depression, psychosis, hearing loss, hepatitis, and kidney impairment are experiences by many patients treated for MDR TB and XDR TB. Directed costs (in 2017) average from $19,000 to treat drug-susceptible TB, $164,000 to treat MRD TB, to $526,000 to treat XDR TB, without counting productivity losses experienced by patients while undergoing therapy.\(^10\)

According to a WHO report in 2015, of the estimated 480,000 individuals with MDR TB globally, only 136,000 were properly diagnosed, 97,000 were started on therapy, and 47,000 were successfully treated. Early and accurate diagnosis and effective treatment of MDR TB reduce the spread of MDR TB and prevent the development of XDR TB.

Table 1 is from CDC Morbidity and Mortality Weekly Report (MMWR) 2003 treatment of Tuberculosis:\(^11\)

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\(^c\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*
Table 1: Anti-TB drugs currently in use in the US

<table>
<thead>
<tr>
<th>Frist-line drugs</th>
<th>Second-line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid <em>(Boxed Warning for hepatitis)</em></td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Levofoxacin*</td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>Moxifloxacin*</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Gatifloxacin*(removed from US market 05/2005)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>para-aminosalicyclic acid</td>
</tr>
<tr>
<td></td>
<td>streptomycin <em>(Boxed Warning for neurotoxicity)</em></td>
</tr>
<tr>
<td></td>
<td>amikacin/kanamycin*</td>
</tr>
<tr>
<td></td>
<td>capreomycin <em>(Boxed Warning for neurotoxicity)</em></td>
</tr>
<tr>
<td></td>
<td>bedaquiline <em>(approved in 2012, not on MMWR, Boxed Warning for increased mortality &amp; QT prolongation)</em></td>
</tr>
</tbody>
</table>

*not approved by the FDA for use in the treatment of TB

Bedaquiline was approved by the FDA 2012 with a Boxed Warning for increased mortality and QT prolongation. The labeling of bedaquiline communicates hepatoxicity in Warnings and Precautions. At the time of approval the Applicant was required to develop a patient registry. The sponsor maintains the patient registry and collect data on indication for use, including utilization of expert medical consultation, minimum inhibitory concentration (MIC) data for baseline and any subsequent MDR-TB isolate (in patients who have relapsed/at end of treatment), drug utilization data, information on the drug distribution mechanisms used, information on how the drug was actually distributed to patients, patient outcomes (clinical and microbiologic), safety assessments in bedaquiline-treated patients, including deaths and concomitant medications. The final report is anticipated in August 2019.

4 Benefit Assessment

Study 1 (NCT02333799) was a multicenter, open-label study conducted in patients with XDR, or treatment intolerant/nonresponsive (TI/NR) MDR pulmonary TB. The patients received Pretomanid (Pa)/Bedaquiline (B)/ Linozolid (L) (BPaL) regimen for 6 months (exendable to 9 months for 2 patients in the study) with 24 months of follow-up. BPaL regimen contains pretomanid 200 mg orally once daily,
bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg three times per week, and linezolid orally 1200 mg once daily or 600 mg twice daily. As of the cut-off date for the interim analysis, 107 of 109 patients completed assessment for the primary efficacy analyses.

Treatment failure was defined as the incidence of bacteriologic failure, bacteriologic relapse, or clinical failure through follow-up 6 months after the end of treatment. Patients considered treatment failures were categorized as having an unfavorable outcome. Table 1 presented the outcomes 6 months after the end of treatment.

Table 1: Outcomes six months after the end of treatment¹

<table>
<thead>
<tr>
<th></th>
<th>total</th>
<th>XDR-TB</th>
<th>TI/NR MDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total accessible</td>
<td>107</td>
<td>71</td>
<td>36</td>
</tr>
<tr>
<td>Favorable (culture negative at 6 month post treatment)</td>
<td>95 (89%)</td>
<td>63 (89%)</td>
<td>32 (89%)</td>
</tr>
<tr>
<td>Unfavorable Death during treatment</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Relapse post treatment (not culture confirmed)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal, loss follow-up/contaminated cultures</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total unfavorable</td>
<td>12 (11%)</td>
<td>8 (11%)</td>
<td>4 (11%)</td>
</tr>
</tbody>
</table>

The favorable outcome was seen in 95 (89%) patinets and unfavorable outcome in 12 (11%) patients. The favorable outcome rate significantly exceeded the historical success rate for XDR-TB based on a lieterature review. The outcomes were similar in both HIV negative and HIV positive patients.

5 Risk Assessment & Safe-Use Conditions

In Study 1, 109 patients were treated with the indicated BPaL regimen and are included in the safety analysis. Of these patients, 76% were black and 23% were of mixed race. Their ages ranged from 17 to 60 years (mean age 36 years), and all patients were from South Africa. Fifty-six percent of the patients were HIV infected. Six (5.6%) patients died during the 26-week treatment period and 2 (1.8%) patients died during follow-up. Treatment emergent adverse events (TEAEs) leading to 6 deaths during the 26-week treatment period included: pneumonia (2 patients), pulmonary TB (2 patients), acute pancreatitis (1 patient), and upper gastrointestinal hemorrhage (1 patient). Two patients died during follow-up, one patient died of natural cause on day 369 and the other patient died of sepsis on day 486.¹²
The followings are the risks associated with combination therapy with pretomanid, bedaquiline, and linezolid; if approved, these risks will be communicated in the warnings and precautions section of the label and are listed below.

Pretomanid will only be indicated for use as part of a regimen in combination with bedaquiline and linezolid. HCPs will be advised to refer to the prescribing information for bedaquiline and linezolid for additional risk information.

5.1 HEPATOTOXICITY

Hepatic-related adverse reactions were reported with BPaL regimen. In Study 1, 27% of patients experienced increased transaminases. There were 2 patients met potential Hy’s law criteria. The liver enzymes of these 2 patients returned to acceptable levels after stopping the therapy. They resumed the BPaL therapy and continue to the end of study.

In 2015, there were 4 deaths due to hepatotoxicity in 2 pretomanid trials other than Study 1; one death in trial NC-005 in a patient treated with the comparator and 3 deaths in trial NC-006 in patients treated with a pretomanid-containing regimen, MPaZ (moxifloxacin 400 mg, pretomanid 200 mg and pyrazinamide 1500 mg). In 2015, NC-005 was placed on partial clinical hold to enrollment of new patients for all study arms until a possible association of pretomanid-containing regimen with hepatotoxicity could be examined. In 2016, the partial clinical hold was removed after additional monitoring for hepatic adverse events and other safety measures were put in place in trial N-005. The results were evaluated by an academic consultant who suspected that the most likely culprit for the hepatotoxicity of the MPaZ regimen was pyrazinamide. Dr. John Senior, from FDA’s Office of Surveillance and Epidemiology (OSE), was consulted regarding the hepatoxic potential of pretamonid. Dr. Senior’s review evaluated 8 deaths in study 1, six during the planned treatment course and 2 that occurred after treatment was completed. None were due to liver failure but were attributed to other causes. Many patients were enrolled with far advanced TB and treatment was started too late. There were no patients withdrawn from the study because of hepatotoxicity, and no death was considered related to drug-induced hepatotoxicity.

The labeling will advise HCPs to monitor for signs/symptoms of liver toxicity and order laboratory tests at baseline, at 2 weeks, and then monthly. Interruption of therapy will be advised if there is evidence of liver injury.

5.2 MYELOSUPPRESSION

\[d\] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Reference ID: 4459411
Myelosuppresion, a known adverse reaction of linezolid, was reported with BPaL regimen. When linezolid dosing was reduced, interrupted, or discontinued, the observed myelosuppression was reversed.

If approved, HCPs will be advised to monitor complete blood counts at baseline, at 2 weeks, and then monthly in patients receiving linezolid as part of the BPaL regimen. Linezolid dosing is to be decreased or interrupted in patients who develop or have worsening myelosuppression.

5.3 PERIPHERAL AND OPTIC NEUROPATHY
If approved, labeling will advise that peripheral and optic neuropathy, known adverse effects of linezolid use, were reported with the BPaL regimen. Neuropathy associated with linezolid is generally reversible or improved with appropriate monitoring and dose interruption, dose reduction, or discontinuation of linezolid. HCPs will be also advised to monitor visual function in all patients receiving the combination regimen. Interrupt linezolid dosing and consult promptly with ophthalmologic evaluation if a patient experiences symptoms of visual impairment.

5.4 QT PROLONGATION
If approved, labeling will advise that QT prolongation, a known adverse effect of bedaquiline, was reported with the BPaL regimen. HCPs will be advised to check ECGs before initiation of bedaquiline, and at least 2, 12, and 24 weeks after starting the combination regimen. Monitoring and correction of serum electrolytes will be recommended.

The prescribing information will further communicate that patients who are receiving bedaquiline as part of the BPaL regimen may have an increased risk for QT prolongation if they have a history of Torsade de Pointes, congenital long QT syndrome, ongoing hypothyroidism, ongoing bradyarrhythmia, uncompensated heart failure, or serum potassium, calcium, and magnesium levels below the normal limits of normal.

5.5 DRUG interaction
Labeling will advise that pretomanid may be in part be metabolized by CYP3A4. HCPs will be advised to avoid co-administration of CYP3A4 inducers, such as efavirenz, during treatment with pretomanid.

5.6 REPRODUCTIVE EFFECTS
Pretomanid caused testicular atrophy and impaired fertility in male rats. In the warnings and Precautions of the labeling, HCPs will be advised to educate patients of reproductive toxicities in animal studies and that the potential effects on human male fertility have not been adequately evaluated.

5.8 LACTIC ACIDOSIS
HCPs will be advised that lactic acidosis, a known adverse reaction of linezolid, was reported with the combination regimen of BPaL. The labeling will recommend that HCPs monitor lactic acid levels, as well as immediately evaluate and interrupt linezolid or the entire regimen if patients develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level.
6  Expected Postmarket Use

Pretomanid will be most likely prescribed, as part of combination regimen that includes bedaquiline and linezolid, by local department of health TB treatment centers and four TB Centers of Excellence. Per CDC TB 101 for Health Care Workers, it will be administered by directly observed therapy (DOT) by a trained health care worker or other designated individual (excluding a family member) who provides the prescribed TB drugs and watches the patient swallow every dose.

7  Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for pretomanid beyond routine pharmacovigilance and labeling.

8  Discussion of Need for a REMS

The Clinical Reviewers recommend approval of pretomanid on the basis of the efficacy and safety information currently available. At the AMDAC meeting, the statistical reviewer concluded the favorable outcome rate for the BPaL regimen was convincingly higher than the prespecified historical control rate of 50%. The clinical reviewer of safety stated that regular monitoring of patients on BPaL for development of optic and peripheral neuropathy (from linezolid), myelosuppression (from linezolid), QT prolongation (from bedaquiline), and hepatotoxicity will be important, if pretomanid is approved.

TB is the world’s leading cause of death from an infectious disease, estimated more than 4,000 people die every day globally due to TB. TB that is resistant to drugs is a growing threat to public health. The current treatment for highly-resistant TB consists of up to 8 drugs, 6 months of daily injections and followed by 12 to 18 months of 5 oral drugs daily. The long and complicated therapies have poor efficacy, in South Africa, pre-bedaquiline era, have about 20% cure rate. Many patients experienced serious side effects, such as depression, psychosis, hearing loss, hepatitis, and kidney impairment. There are few trials to guide treatment for durg-resistant TB. A new regimen that shortens treatment duration, simplifies administration, has an improved side effect profile, and improves cure rates is needed.

DRISK and DAIP have determined that a REMS is not necessary to ensure the benefits of pretamonid outweigh its risks. The prescribing information will be used to communicate the safety issues and management of toxicities associated with the BPaL regimen. The prescribing information includes LPAD language: has “Limited Population: Pretomanid is indicated, as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of XDR, treatment-intolerant or nonresponsive MDR TB” as well as a “Limitations of Use: Pretomanid is not indicated for patients with drug-sensitive TB, latent infection due to Mycobacterium tuberculosis, extra-pulmonary infection due to Mycobacterium tuberculosis, or MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy”. A Medication Guide as part of labeling is proposed to communicate to patients that pretomanid should only be taken as part of a regimen with bedqauline and linezolid.
The most concerning adverse reaction associated with the use of pretamonid is hepatotoxicity. There were 2 patients who met potential Hy’s law criteria in Study 1. The liver enzymes of these 2 patients returned to acceptable levels after stopping the therapy. They resumed the BPaL therapy and continue to the end of study. Dr. Senior’s review evaluated 8 deaths in study 1, six during the planned treatment course and 2 that occurred after treatment was completed. None were due to liver failure but were attributed to other causes. Many patients were enrolled with far advanced TB and treatments were started too late. The labeling will advise HCPs to monitor for signs/symptoms of liver toxicity and order laboratory tests at baseline, at 2 weeks, and then monthly during treatment.

Other concerning risks associated with BPaL regimen are myelosuppression, peripheral/optic neuropathy, QT prolongation, reproductive effects, and lactic acidosis. These risks will be communicated in the labeling. Myelosuppression, peripheral/optic neuropathy, and lactic acidosis have been reported in patients receiving linezolid. With appropriate monitoring and interruption or reduction linezolid dosing, these adverse effects are reversible or improved. QT prolongation is a known adverse effect of bedaquiline. With ECG and laborotory monitoring, this adverse effect can be mitigated. Pretomanid caused testicular atrophy and impaired fertility in male rats. Male patients of reproductive potential will be advised in labeling of this adverse effect in animals and labeling will also note that the potential toxicity on human male fertility has not been evaluated. At the late cycle meeting with the sponsor, DAIP informed the sponsor that a study report and datasets for the human semen analysis will be requested as one of the potential postmarketing requirements.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for pretomanid to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

1 Draft pretomanid prescribing information 12.4 Microbiology, Mechanism of Action 07/07/2019


3 Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America, MMWR recommendations and reports, June 20, 2003

4 Mase, S, Chorba T, et al Provisional CDC guideline for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis, cdc.org, MMWR 2013; 62 (No. 9)


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15 Daniel, R Pretomanid presentation of clinical efficacy in Antimicrobial drugs advisory committee meeting, 06/06/2019

16 Zyvox (linezolid) prescribing information, 02/2018

17 Sirturo (bedaquiline) prescribing information, 12/2015


19 Directly Observed Therapy, TB 101 for Health Care Workers www.cdc.gov, accessed 07/01/2019
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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