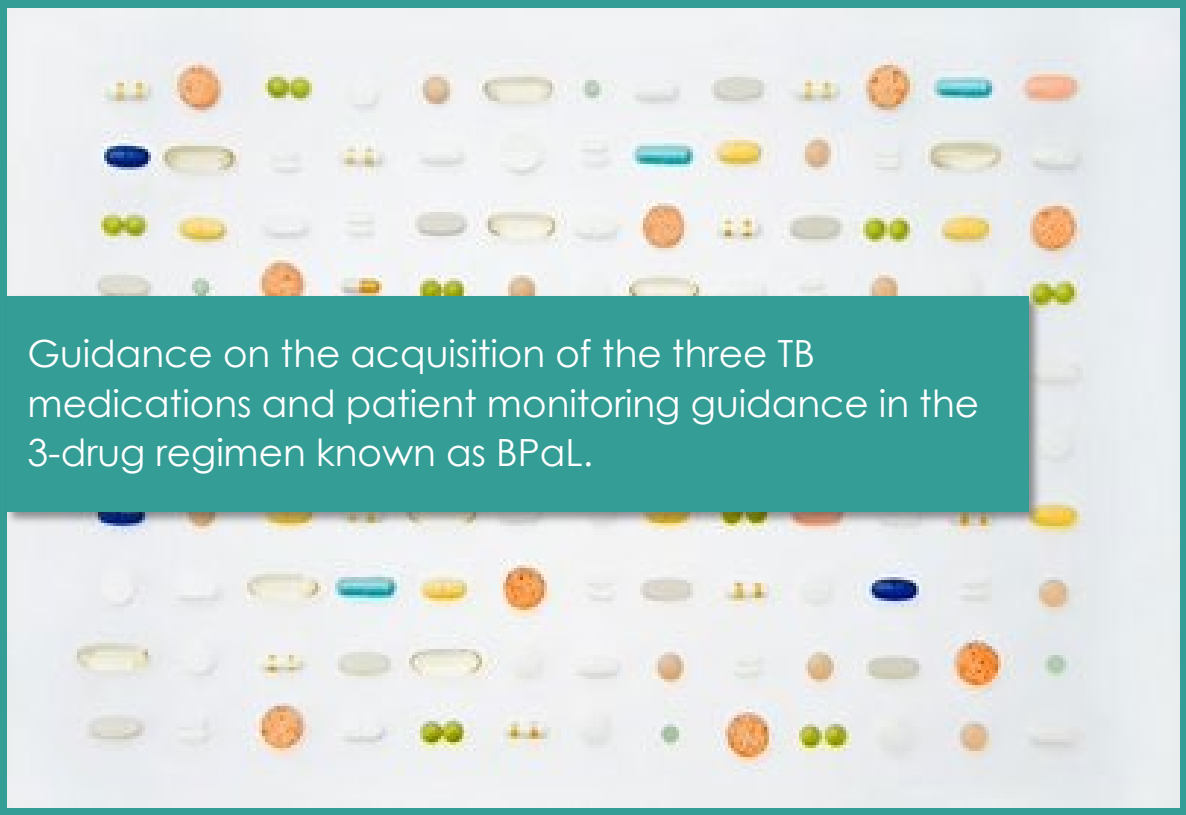
BPaL Guidance

2023



Guidance on the acquisition of the three TB medications and patient monitoring guidance in the 3-drug regimen known as BPaL.

Washington State Department of HEALTH

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Background Information on BPaL

Terminology

Drug Classes						
CDC resistance classification[1]		**Isoniazid & Rifampin**	**Fluoroquinolone (at least one)**	**Second-line injectable (at least one)**	**Bedaquiline (BDQ)**	**Linezolid**
MDR TB		X				
Pre-XDR TB		X		X		
		X	X			
XDR	**Pre-2022[2]**	X	X	X		
	Post-2022[3]	X	X		X	
		X	X			X

[1]Each row indicates one combination of drug resistance that meets the respective definition of pre-XDR or XDR TB.
[2]Although WHO abandoned this row definition in its 2022 update due to the movement away from use of injectables as a routine part of MDR treatment, CDC has retained this as one of three definitions for XDR.
[3]BPaL would not be appropriate for use in XDR that includes resistance to BDQ or linezolid.

Clinical Research

The Nix trial in South Africa demonstrated that 98 (90%) of 109 patients had favorable outcomes with a six-month, all-oral regimen of **bedaquiline** , **pretomanid** and **linezolid (BPaL)** for treatment of tuberculosis (TB) that was extensively drug-resistant (XDR—as defined at that time), multidrug-resistant (MDR) TB that was not responsive to treatment, or for MDR TB in which a second-line regimen had been discontinued because of side effects. Although not a head-to-head trial against the standard 18–24-month regimens for MDR TB, BPaL's results were much better than those previously obtained with these longer regimens. However, peripheral neuropathy (81%) and myelosuppression (48%) associated with the 1200mg daily dose of linezolid were common.

A subsequent Zenix trial examined the safety and efficacy of BPaL using four different combinations of linezolid dosing and duration (600mg vs 1200mg daily and 9 weeks vs 24 weeks) in an effort to recreate the favorable efficacy outcomes from the Nix trial while potentially reducing linezolid-associated adverse effects. Again, enrolled patients were those with XDR-TB (as defined at that time), MDR-TB that was not responsive to treatment, or MDR-TB for which a second-line regimen had been discontinued because of side effects. Similar to findings from the previous trial above, 84%-93% of patients in the Zenix trial had favorable outcomes, with the lowest favorable outcome rate seen in the linezolid 600mg x 9-week group. The overall risk–benefit ratio favored the group that received linezolid at a dose of 600 mg for 26 weeks, with 89% favorable outcomes, a lower incidence of peripheral neuropathy reported (24%), and fewer linezolid dose modifications required (13%).

The PRACTECAL study added moxifloxacin (M) to make a 6-month BPaLM regimen and compared it head-to-head against standard, 9-20 month MDR regimens (but not head-to-head against BPaL itself) among patients with rifampin-resistant TB (with or without resistance to additional drugs). Favorable outcomes were observed in 89% of BPaLM recipients versus 52% of standard MDR treatment recipients.

Safety outcomes were also better in the BPaLM group. No data were available to demonstrate the marginal benefit of BPaLM over BPaL because there was no BPaL arm in the study.

Regulatory Framework

- BDQ was approved by the Food & Drug Administration (FDA) at the end of 2012 for the treatment of adults with MDR pulmonary TB for whom an effective treatment regimen is not otherwise available.
- Linezolid was approved by the FDA in 2002 for use in a variety of infections. Its use in drug-resistant (DR) TB is off-label yet at the same time implicitly endorsed in FDA's approval language for pretomanid.
- Pretomanid was approved by the FDA in 2019 for use in combination with BDQ and linezolid (BPaL) in adults with pulmonary XDR as well as in patients with treatment-intolerant or -nonresponsive MDR TB.
- Moxifloxacin was approved by the FDA in 2000 for use in a variety of infections. Its use in DR TB is off-label.

Clinical Guidance and Recommendations

On May 4, 2022 the CDC updated BPaL guidance originally released February 2, 2022, echoing FDA's approval language for pretomanid and recommending use of the BPaL regimen for adults with pulmonary MDR that is also resistant to one fluoroquinolone and/or injectable agent, as well as treatment-intolerant or treatment-nonresponsive MDR TB. CDC's BPaL guidance emphasized the following key points:

- A physician with expertise in DR TB treatment should be involved in the patient's treatment plan.
- An initial linezolid dose of 600 mg should be used when using the BPaL regimen in the treatment of adults.
- Treatment with BPaL can be extended to 9 months (39 weeks) based on delayed treatment response within the first 8 weeks (e.g., culture conversion after 8 weeks, delayed clinical improvement, and other underlying clinical factors).
- FDA has not approved pretomanid for use in extrapulmonary TB nor has it approved pretomanid use in regimens other than BPaL.
- This guidance is based on clinical trials with small numbers of enrollees; rare adverse events may be detected as more patients use the BPaL regimen.

The Curry International TB Center at the University of California San Francisco (CITC), one of CDC's four centers of excellence in TB education, training, and consultation, endorses and provides clinical guidance on use of BPaL/BPaLM, including its off-label use under appropriate circumstances and in concert with expert consultation and proper monitoring.

In its 2022 update to treatment of drug-resistant TB, the World Health Organization suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, and linezolid (600 mg) (BPaL) rather than previous standardized or individualized regimens in MDR or rifampin-resistant cases and further recommends the addition of moxifloxacin (BPaLM) if the organism is sensitive to fluoroquinolones.

Programmatic Evaluation of BPaL Implementation

Data from U.S. patients treated with BPaL between 10/14/2019 and 4/30/2022 were compiled and analyzed by the BPaL Implementation Group (BIG), including baseline examination and laboratory, electrocardiographic, and clinical monitoring throughout treatment and follow-up. The evaluation included patients with features outside the FDA approval (i.e., off-label use), including any rifampin resistance/MDR (common), as well as rare cases involving rifampin intolerance, extrapulmonary disease,

and adolescence. Approximately 10% of this cohort were Washington State cases. Of 70 patients starting BPaL, two changed to rifampin-based therapy, 68 (97.1%) completed BPaL, and two of these 68 (2.9%) patients relapsed after completion. Using an initial 600 mg linezolid dose daily adjusted by therapeutic drug monitoring and careful clinical and laboratory monitoring for side effects, supportive care, and expert consultation throughout BPaL treatment, three (4.4%) patients with hematologic toxicity and four (5.9%) with neurotoxicity required a change in linezolid dose or frequency. The median BPaL duration was 6 months. BIG authors concluded that BPaL has transformed treatment for rifampin-resistant or -intolerant TB and that the experience with this cohort demonstrates that its early implementation is feasible.

In the rare patient who has relapsed thus far after completing BPaL, acquisition of reduced sensitivity to BDQ (i.e., increased minimum inhibitory concentration [MIC]) has been noted. At least one United States case of BDQ resistance has been detected in a previously untreated patient from a former Soviet republic where BDQ has been in use. This points to the importance of vigilance for the emergence of resistance to this and other drugs in the regimen as BPaL implementation moves forward.

Summary

A 6-9 month regimen of BPaL in concert with expert medical and nursing consultation, reference mycobacteriologic studies, therapeutic drug monitoring, and careful clinical monitoring affords safety and efficacy in the treatment of rifampin-resistant and rifamycin-intolerant TB that makes it the emerging preferred approach to the management of such cases. Moxifloxacin may add marginal net benefit to BPaL under certain circumstances (e.g., extensive disease, heavy bacillary load) that can be addressed through expert consultation. The following guidance addresses drug procurement and regimen administration-and-monitoring to complement expert consultation and to further BPaL's implementation in a manner that optimizes personal health and disease control outcomes among such cases in Washington State.

BPaL Medication Overview

RCW 70.30.045: Expenditures for tuberculosis control directed—Standards—Payment for treatment. (wa.gov)

"Tuberculosis (TB) is a communicable disease and TB prevention, treatment, control, and follow-up of known cases of tuberculosis are the basic steps in the control of this major health problem. In order to carry on such work effectively in accordance with the standards set by the secretary under RCW **70.28.025**, the legislative authority of each county shall budget a sum to be used for the control of TB, including case finding, prevention, treatment, and follow-up of known cases of TB. Under no circumstances should this section be construed to mean that the legislative authority of each county shall budget sums to provide tuberculosis treatment when the patient has the ability to pay for the treatment. Each patient's ability to pay for the treatment shall be assessed by the local health department." *(underline in quote above added by WA DOH TB Program).*

It is recommended that all three medications be started at the same time. If there is a delay in receiving any one of the medications, it will impact your patient's treatment start date. Bedaquiline will typically take the longest to get approved. Case managers, please advise your patients that BPaL medications take extra time, up to a week or more, to arrive.

Keys:

- Read through this document and the NTCA guidance on the NTCA website to gather all the information that will be needed and to familiarize yourselves with the potential requirements and processes. Each of the 3 medications are acquired in different ways.

- Like any medication purchased through the King County pharmacy, once an LHJ opens a bottle it cannot be returned to the pharmacy to be redistributed to another LHJ.

- **If the medication did not originally come through the King County pharmacy**, it cannot be returned to them for distribution to other LHJs.

- Discuss with a DOH Nurse Consultant to join the ***Longitudinal Case Consultation Panel*** monthly meetings for expert MDR treatment guidance that includes both nursing and physician support. Expert consultation is recommended for the management of any multi-drug resistance case.

- When communicating with Health Care Authority (HCA) about a denial, state that a prescription or service was **denied** and include the demographic info (such as name, DOB, Provider 1 #, Insurance Company (MCO) Name, and claim # if available). HCA will create a *ticket* with this information, and it will be assigned to someone to work on it. The best email is applehealthpharmacypolicy@hca.wa.gov.

Accessing Bedaquiline (Sirturo)

Metro Medical
Only way to access to bedaquline
(See weblink in below in Keys)
pharmacy direct number 866.716.5486;
client services 800.768.2002
email: CustomerSvc@metromedical.com
LHJ will need the LHJ's Tax ID and Provider's NPI #

It is crucial that you read both this document and the NTCA Guidance document. This graphic is only an overview and is missing essential details.

Ensure Metro Medical prescription is correctly written
The prescription for all 6 months will be seperated into 3 items on a single Rx form
(See Example on Page 10 in this document)

Sirturo is on the HCA Medicaid formulary as a *preferred* medication

Janssen's CarePath
for patients with insurance
Metro Medical will contact patient's insurance regarding co-pay coverage
Metro Medical will connect you/your patient to issue a CarePath co-pay assistance card

No income verfication needed

Call Janssen's CarePath if you haven't heard back in **24 hours**

Johnson & Johnson Patient Assistance Foundation (JJPAF)
(See link to Application Form below in Keys)
for patients with and without insurance

HCP will need to complete Sirturo prescription for the entire 6 month treatment on pg 3 of application (example in Appendix A)
FAX completed form to Johnson and Johnson at 1-888-526-5168.

Assistance Diversion Programs are prohibited by Janssen to participate; some insurance documentation may be required
Sirturo does not require a federal tax return.

JJPAF gives you
Retail Card #, Group # and BIN # (all 3 are required). Give all three of these numbers to Metro Medical to process your medication order (ask, this may change)

Follow up with JJPAF if you haven't heard from them in **24 hours**.
1-833-742-0791

Bedaquiline (Sirturo) (BDQ)

400mg QD for 2 weeks (14 doses) followed by 200 mg 3 times a week (72 doses over 24 weeks) for a total of 26 weeks
(total of 86 doses over 26 weeks)

***Note:** No dose modifications allowed. Check with a TB Expert for pediatric dosing.

The manufacturer of BDQ has a special contract in place with Metro Medical to be the sole distributor of the drug to the US market. In Washington depending upon insurance status there are different pathways to obtaining this medication. Metro Medical will contact the patient's insurance company (whether private or state insurance) to determine coverage and associated co-pays.
An eligible patient does **not have to be a** US citizen or legal resident to participate in these assistance programs. But the patient does need to live in US or US territory and be treat by US physician as outpatient.

Before contacting Metro Medical, gather **all** the information required so missing information doesn't slow down the process and ensure that the patient has completely filled-out any required information. (See page 10 of the NTCA Access Guide for list of required information).

Washington State's Health Care Authority (HCA) is working with all their Managed Care Organizations to include Metro Medical (out-of-state distributor) for Washington's Medicaid patients to access BDQ.

Keys:

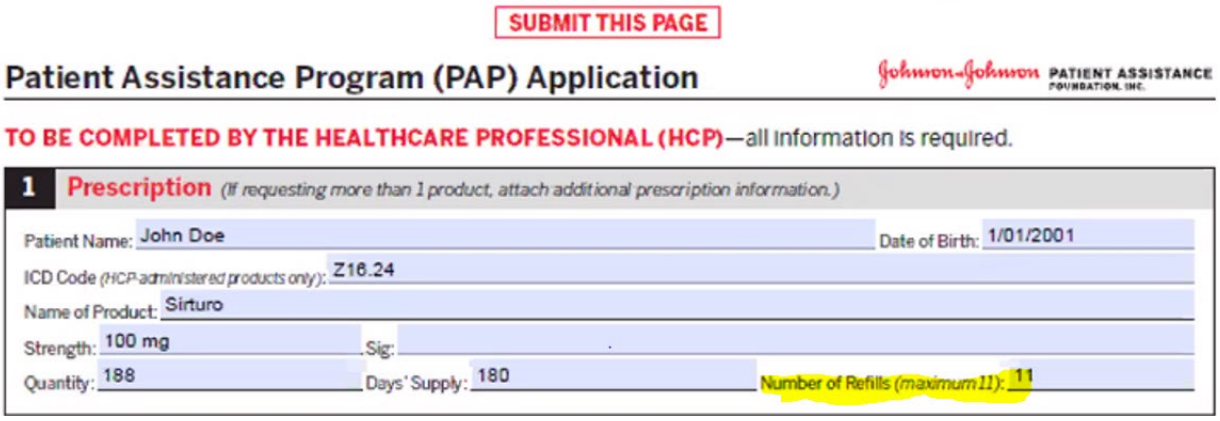
- The ordering prescriber must match the MD on the application.
- Johnson & Johnson and Metro Medical will authorize and deliver only to an outpatient pharmacy, but a hospital's outpatient pharmacy will be accepted.
- You must go through Metro Medical/Cardinal Health to access BDQ. Ingrid Glasper, Manager customer service, ingrid.glasper@cardinalhealth.com
- Ensure that the Metro Medical prescription is written as shown in the example below pm page 8. This is different from how the prescription section of the JJPAF application is completed.
- Because Johnson and Johnson revise the application forms *frequently,* download a new application each time.
- Order the maximum refills allowed under the program.
- Going through Metro Medical is the only way to access CarePath assistance to cover BDQ cost.
- If you haven't heard back in **1 business day** from Metro Medical, Janssen's CarePath, or JJPAF call them back. Reach out to the WA TB Program as well at TBServices@doh.wa.gov as soon as you feel there is a delay.
- Once your application has been approved, you contact Metro Medical to let them know your patient has been approved and you provide Retail Card #, Group # and BIN # (all 3 are required) --all three should have been given to you J&J/Janssen (ask, this may have changed and may not be needed). These 3 key pieces of crucial information will also be faxed to the LHJ/Provider.
- **Do not accept any rejection** of your application – there is an established precedent for providing BDQ assistance for free when a TB program risks depleting its funds in order to pay for BDQ. It is

Janssen's position that TB programs should never have to use their funds to pay for this medication.

Manufacturer Assistance Programs for Patients

Patients with limited income and insurance or no insurance can use JJPAF
Application form & Application Guidance

For uninsured patients complete this form including this prescription information **requesting the maximum number of refills**.



SUBMIT THIS PAGE

Patient Assistance Program (PAP) Application

Johnson & Johnson PATIENT ASSISTANCE FOUNDATION, INC.

TO BE COMPLETED BY THE HEALTHCARE PROFESSIONAL (HCP)—all information is required.

1 Prescription *(If requesting more than 1 product, attach additional prescription information.)*

Patient Name: John Doe Date of Birth: 1/01/2001

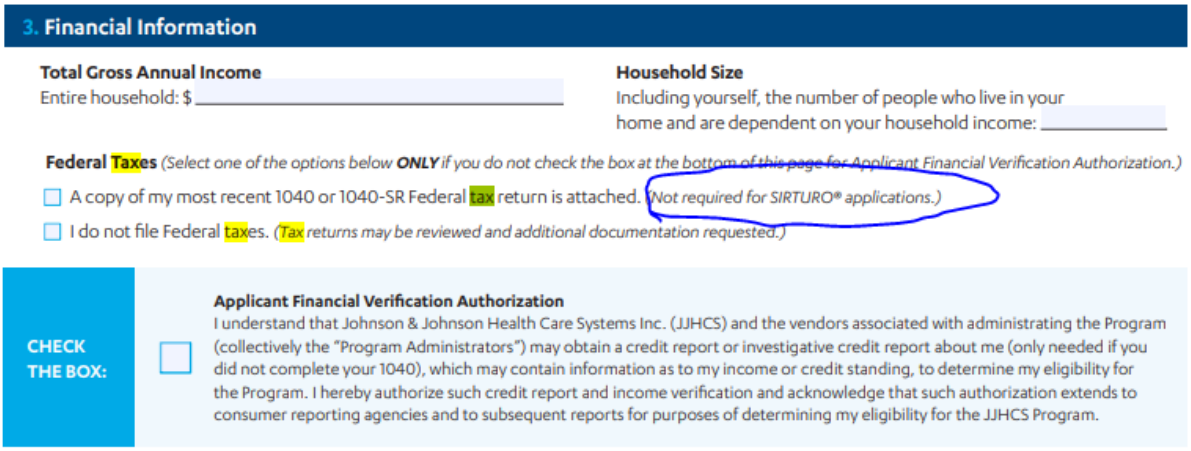
ICD Code *(HCP-administered products only)*: Z16.24

Name of Product: Sirturo

Strength: 100 mg Sig:

Quantity: 188 Days' Supply: 180 Number of Refills *(maximum 11)*: 11

Make sure to highlight/circle that Bedaquiline/SIRTURO applications do not require tax information.



3. Financial Information

Total Gross Annual Income
Entire household: $ _____

Household Size
Including yourself, the number of people who live in your home and are dependent on your household income: _____

Federal Taxes *(Select one of the options below **ONLY** if you do not check the box at the bottom of this page for Applicant Financial Verification Authorization.)*

☐ A copy of my most recent 1040 or 1040-SR Federal tax return is attached. *(Not required for SIRTURO® applications.)*

☐ I do not file Federal taxes. *(Tax returns may be reviewed and additional documentation requested.)*

CHECK THE BOX: ☐

Applicant Financial Verification Authorization
I understand that Johnson & Johnson Health Care Systems Inc. (JJHCS) and the vendors associated with administrating the Program (collectively the "Program Administrators") may obtain a credit report or investigative credit report about me (only needed if you did not complete your 1040), which may contain information as to my income or credit standing, to determine my eligibility for the Program. I hereby authorize such credit report and income verification and acknowledge that such authorization extends to consumer reporting agencies and to subsequent reports for purposes of determining my eligibility for the JJHCS Program.

TO BE COMPLETED BY HEALTHCARE PROVIDER: All information is required.

1. Prescription *(Please complete a copy of this page for each medication and dosage strength you are requesting.)*

Patient First Name: _____ Patient Last Name: _____

Date of Birth (*mm/dd/yyyy*): _____ ICD Code: _____

Name of Product: _____ Strength: _____

Sig: _____ Quantity: _____ Day Supply: _____

First Time Fill: ☐ Yes ☐ No Number of Refills (*maximum 11*): _____ Anticipated 2023 First Fill Date: _____

Patient Allergies: _____ or ☐ none

List of Patient's Current Medications: _____ or ☐ none

For SPRAVATO®: Due to the product being a controlled substance, an Rx cannot be captured in the Patient Enrollment Form. An electronic prescription must be sent to "*Wegmans Specialty Pharmacy #198*" directly from the HCP.

For PONVORY®: Before initiation of treatment with PONVORY®, you are required to assess the patient's individual needs for completion of pretests. If this has been completed, please check the box below. We are unable to dispense PONVORY® for your patient until this step has been completed.

☐ I attest that I have assessed the following based on individual patient needs: Complete Blood Count, Cardiac Evaluation, Liver Function Tests, Ophthalmic Evaluation, Current or Prior Medications with Immune System Effects, and Vaccinations. This patient is cleared to initiate therapy with PONVORY®.

Janssen's CarePath copay coverage

If BDQ is not fully covered by your patient's insurance, there is an assistance program available for coverage of co-pays up to $7500. The co-pay program is called Janssen's CarePath. Ask Metro Medical about CarePath, they are responsible for connecting the TB program or patient to access the Janssen CarePath co-pay assistance card.

Packaging issue:

You will need 200 tablets of BDQ and if you purchase a full bottle it may be packaged with only 188 pills. Mention the exact quantity of pills your patient needs when speaking with Metro Medical. BDQ was originally packaged for a 24-week regimen but BPaL requires 26 weeks to completion. An extra bottle of BDQ will need to be ordered. Typically, BDQ has a two-year expiration date.

Writing Metro Medical Services Prescription:

Example of prescription from Washington State Pharmacy Association:

26 treatment weeks total (200 tablets)
If your patient's treatment is extended the approved application is good for a year.

- 400mg daily for two (2) weeks (56 tablets)
- 200mg three (3) times a week for 24 weeks (144 tablets or 36 tablets + three (3) refills.)

ITEM #	MEDICATION	QTY	DIRECTIONS FOR USE (For BPaL Rx = 26 treatment weeks total, 200 tablets)
Other	Sirturo 100mg tabs (NDC:59676-0701-01)	56	400mg daily for two (2) weeks (56 tablets)
Other	Sirturo 100mg tabs (NDC:59676-0701-01)	144 tablets or 36 tablets plus 3 refills	200mg three (3) times a week for 24 weeks
Other			

ICD 10 Code for Johnson & Johnson Patient Assistance Foundation (JJPAF) Application: **A 15.9**

2023 ICD 10 Codes for TB and MDR TB

Accessing Pretomanid

It is crucial that you read through both this document and the MPPAP Application directions as this page is only overview graphic and there are other details provided elsewhere.

Ensure prescription is correctly written:

200 mg once daily for 26 weeks
No dose modifications allowed

Patients with prescription drug coverage

Access through your patient's local pharmacy or LHJ's drug wholesaler

Prior Authorization needed from insurance company

As of February 7, 2022 pre-authorization is no longer required in the HCA Medicaid Formulary

Currently a "drop ship" item at Cardinal Health

Uninsured or Insured without drug coverage*

Mylan Pretomanid Tablets Patient Assistance Program (MPPAP)

Customer Service 800-796-9526

Mylan Pretomanid Tablets Patient Assistance Program (MPPAP) Eligiblity

Patient must be a US citizen or legal resident living in US

Annual gross household income below 400% FPL (Verification required)
*Patient must meet <u>one</u> of the following (verification for either required):

- No prescription insurance coverage of any type **or**
- has **Commercial** prescription drug coverage **only** for **generic** products (No State or Federal insurance programs such as Medicaid, Medicare, or Tricare)

Patient & provider both certify that they will not submit a claim or resell, trade or barter for a credit for any free product received through MPPAP.

Approved applications: Drugs will be shipped to LHJ free of charge

Pretomanid

200 mg once daily for 26 weeks (200mg tablet) ***Note:** No dose modifications allowed. Check with a TB Expert for pediatric dosing.

Pretomanid is a nitroimidazole, a class of novel anti-bacterial agents. Pretomanid has been developed by TB Alliance and is approved by the US FDA to treat XDR-TB or treatment-intolerant/non-responsive MDR-TB**, ONLY** in combination with BDQ and linezolid, as part of the BPaL regimen.

- Pretomanid is now a preferred medication in the HCA Medicaid formulary.
- **Insurance company Prior Authorization is needed.** Include the ICD-10 diagnostic codes to validate MDR status and a copy of the MD's written prescription showing it will be administered along with Linezolid and Bedaquiline.
- Quick acquisition might be difficult if a patient has prescription coverage and does not qualify for the Mylan Pretomanid Tablets Patient Assistance Program (MPPAP).
- Pretomanid is currently a "drop ship" item, the patient's pharmacy may be reluctant to order if they have to pre-pay for medication. Be aware it has a 3-5 business day delivery time frame.
- The LHJ may be responsible for full amount or the co-pay (amount depends on insurance coverage).
- If patient does not have a regular pharmacy (easiest) then reach out to an FQHC or an independent community pharmacy (e.g. Health Mart, Health Atlas, Bob Johnson's in Seattle).
- The WA Pharmacy Association can assist in finding a pharmacy. See contact information below.

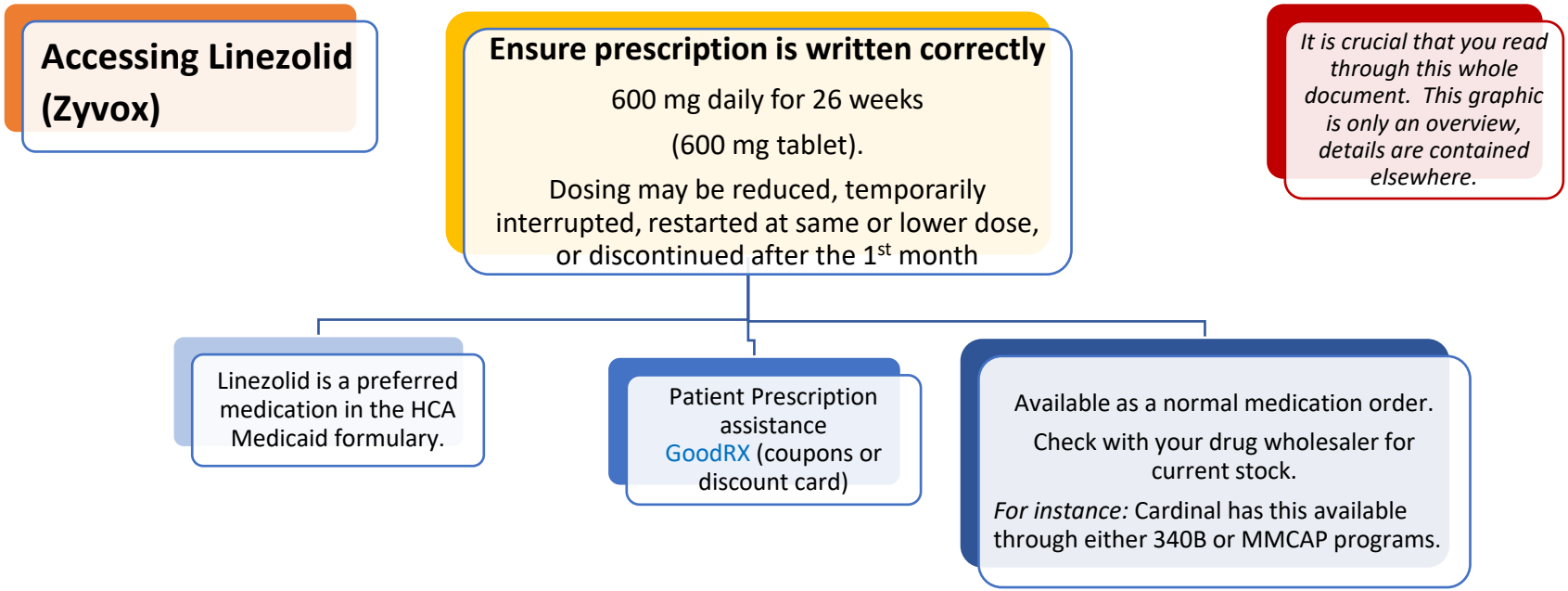
Manufacturer Assistant Program
To participate in the Mylan Pretomanid Tablets Patient Assistance Program (MPPAP): An eligible patient does **not have any** prescription drug coverage and **must be** a US citizen or legal resident.

MPPAP Customer Service Phone: 1.800.796.9526
Contact customer service to receive application form.
(Occasional reminder calls to Customer Service may help expedite)
FYI: Due to a merger, Mylan has changed their name to Viatris, so you may see either name.

Email/Mail or Fax application to:
781 Chestnut Ridge Road
Morgantown, WV 26505
Fax: 1.877.427.7290
Email: MylanPAP@mylan.com

Medication will be shipped in 24-48 hours directly to the ordering LHJ's TB clinic. MPPAP approval lasts one year. The patient is eligible to receive replenishment medication during that year. Replenishment Authorization (form submitted by physician) approval will be considered on an 'as needed' basis.

If a pharmacy is resistant to ordering a dropship medication you can receive assistance setting this up with the receiving pharmacy by contacting:
The **Washington State Pharmacy Association**
Phone: 425-228-7171 / Fax: 425-277-3897
askwspa@wsparx.org



Linezolid (Zyvox)

600 mg daily for 26 weeks (600 mg tablet). Dosing may be modified, temporarily interrupted and restarted at the same or different dose, or permanently discontinued depending on clinical tolerance and therapeutic drug monitoring results. ***Note: Check with a TB Expert for pediatric dosing.**

- Linezolid is a preferred medication in the HCA Medicaid formulary.
- Ask pharmacy to check with their drug wholesaler for current stock. For example, Cardinal Health has it listed available through either 340B or the MMCAP programs.
    - If your LHJ doesn't have accounts set up to access the medication, please reach out to us at: TBServices@doh.wa.gov

Note: **Linezolid doses in this regimen are less than what is typically used for other diseases.** 600 mg daily is less than the linezolid dose used in Nix (1200 mg daily). See background section above regarding the evidence base for this initial linezolid dosing strategy. The 600 mg daily dose may be modified in strength or frequency based on results from therapeutic drug monitoring and clinical tolerance (*see* below).

Patient Monitoring and Dosing Information

Most of the information in this section is from the Curry Drug Resistant TB Survival Guide, 3rd Edition

- ADVISE PATIENTS TO AVOID BECOMING PREGNANT.
- In the NIX study, medication was administered orally, with food.
- In NIX, if a patient was still culture positive between 4 and 6 months of treatment, they were given an additional 3 months of treatment.
- Cultures should be done frequently to document when patient has converted to culture negative. Start every 1-2 weeks initially, then decrease frequency to monthly. (See table below: **Activities for monitoring treatment response for MDR-TB** Table 1: Curry Survival Guide, pg.204)

Baseline examinations

Laboratory exams: HIV test, CBC, TSH, pregnancy test for people of childbearing age, and a comprehensive metabolic panel). Some experts also recommend performing baseline, monthly and prn magnesium and lipase levels. Hypomagnesemia can lead to other electrolyte (potassium, calcium) disturbances that predispose to QTc prolongation or ill effects thereof. Lipase elevations can signal pancreatitis which has been described as a rare adverse effect of pretomanid. **Curry Guide Tool 4: *Laboratory Flow Sheet*** may be helpful in summarizing bloodwork results that will be assessed at baseline and throughout treatment.

Vision (acuity and color), **and vestibular function** should be assessed at baseline and results documented. The Curry Survival Guide **Tool 5: *Vision Screening Flow Sheet*** and **Tool 6: *Hearing and Vestibular Flow Sheet*** may be helpful for tracking these serial monitoring results. Optic neuritis is a known adverse effect of linezolid that should be carefully monitored for. Audiovestibular toxicity is not a typically anticipated consequence of the drugs in the BPaL regimen and some experts question whether this monitoring is necessary in patient on BPaL who do not report hearing or balance disturbance.

Radiography should be obtained prior to treatment initiation unless the most recent prior chest radiograph is less than two weeks old. Posteroanterior (PA) views (and lateral in children) of the chest for pulmonary disease are recommended. Additional views and/or CT scan may be helpful in some instances.

Sputum for nucleic acid amplification test (NAAT), acid-fast bacilli (AFB) smear, culture, and drug-susceptibility testing (DST—both molecular and phenotypic): At the start of treatment, obtain 3 sputa for AFB smear and culture.

Important note: In a patient started on a standard TB regimen (RIPE) for 4 weeks or more prior to starting an MDR-TB regimen and for whom the initial isolate was not known to be resistant to **all** first-line drugs at baseline, request a repeat DST from a subsequent positive TB culture obtained near the time of MDR-TB regimen initiation. This will help to detect any additional resistance acquired during the initial period of therapy.

Consult with WA DOH TB Program to ensure that the most appropriate specimen and/or isolate is forwarded to national mycobacteriology reference laboratories for molecular detection of drug

resistance, phenotypic drug susceptibility testing, and minimum inhibitory concentration (MIC) levels for drugs in the regimen. Often several such laboratories will become involved and produce a constellation of results from which a consensus impression is derived.

For more information on drug susceptibility testing see: At-a-Glance: Drug Susceptibility Testing Available at 5 US Referral Laboratories. For the full version, Excel spreadsheet: Drug susceptibility testing available at 5 U.S. referral laboratories (updated: June 24, 2022. Please check often for updates.)

For more background on MICs and other aspects of DSTs and mycobacteriology, see Laboratory, Chapter 3 in Drug Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd ed.

For documentation **Curry Survival Guide Tool 3: *Bacteriology Flow Sheet*** may be helpful for summarizing the important mycobacteriology, molecular tests, and DST results.

EKG: For patients who will be taking BDQ, a baseline EKG is recommended. Coordinate EKG monitoring either with outside providers, at the TB clinic, or utilize remote/mobile monitors after baseline. If with outside providers/clinics, make sure to address isolation issue, if applicable. Not all clinics have isolation exam rooms.

Plan ahead for repeat EKGs at 2-weeks, 4-weeks, and then monthly while on treatment. For individuals with risk factors for QTc prolongation check weekly for several weeks until stable then continue no less than monthly. Seek expert consultation and cardiology consultation urgently if QTc exceeds 500ms or if the patient develops an arrhythmia or symptoms thereof. This will usually call for withdrawal of QTc prolonging drugs.

Starting a patient on a potentially QTc prolonging drug should only be done after careful history to determine risk for QTc prolongation. Commonly prescribed drugs can cause QTc prolongation. If the patient is on other QTc prolonging drugs or has a dysrhythmia (or risk factors for one) then a cardiology consultation is strongly advised. Discussion with the patient around benefits and risk of the treatment is very important and documentation of informed consent is key.

For more information see:

- Guide for QTc Monitoring and Management of Drug-resistant TB Patients with QT-prolonging Agents
- Options for Obtaining Mobile Electrocardiogram (EKG) in Washington State.
- Mayo QTc calculator – a tool to calculate the QTc using numbers from an EKG or mobile EKG device.
- https://www.crediblemeds.org - a website to look up QTc prolonging drugs, the more drugs the person is on with this side effect the more likely they will have a life-threatening QTc prolongation.

Psychosocial assessment: Assess for existing mental health and social conditions that may impact treatment. See the Curry Survival Guide section: Psychosocial Support and Resources for Behavioral and Cognitive Health Assessment (sharepoint.com).

Therapeutic Drug Monitoring (TDM)

One of the BPaL drugs, linezolid, is effective but carries a risk of concentration-related and mitochondrial-mediated adverse drug reactions (i.e., neuropathy and cytopenias). The Curry International TB Center and many other experts conducting TDM for linezolid among patients on BPaL. TDM allows clinicians to balance the competing goals of giving enough of a drug to kill the bacteria that cause TB while not harming the patient. (There is no consensus on the use of TDM for BDQ or pretomanid.)

The typical approach is to check trough (i.e., immediate pre-dose), 2-hour, and 6-hour linezolid levels at approximately two weeks into treatment. The lab measures drug concentrations in the patient's serum and then may recommend adjustments to the size or frequency of the doses. This approach gives the clinician information on the kinetics of a patient's absorption, metabolism and clearance of a drug. That, in turn, allows them to find the right dose early during treatment and optimize outcomes. Some TDM service providers (e.g., University of Florida Infectious Diseases Pharmacokinetics Laboratory) will offer recommendations on dosing along with the results.

The typical target for a 2-hour linezolid peak is 12-26 ug/mL, with an attendant objective of achieving a peak serum level-to-MIC ratio in the range of 4:1-to-16:1. Achieving these targets indicates adequate linezolid exposure for mycobacterial killing. The target for the 24-hour post-dose trough is <2ug/mL because the incidence of neuropathy and bone marrow suppression is greater when the trough is above this level. The standard approach to a low peak level is to increase the dose (e.g., from 600mg/day to 900mg/day), whereas the approach to a high trough is to increase the dosing interval (e.g., from daily to three times weekly [qMWF]). Follow-up levels are usually repeated 2-3 weeks after a dosing change to assess whether target levels have been achieved. Consult an MDR expert for further guidance in the conduct, interpretation and response to therapeutic drug monitoring results.

For more background on TDM, see Laboratory, Chapter 3 in Drug Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd ed.

WA DOH TB Program at: TBServices@DOH.WA.GOV; 206-418-5500 for guidance in the collection and submission of specimens for therapeutic drug monitoring.

Activities for monitoring treatment response for MDR-TB

Monitoring evaluation	Recommended frequency
Evaluation by clinician	• **During the intensive phase:** Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. • Once stable, the patient is seen twice a month or once a month. • **During the continuation phase:** Monthly assessments unless there is a medical necessity to see the patient more often. The DOT provider sees the patient daily between consultations and signals any concerns to the case manager and clinician.
Treatment adherence and tolerance	• Daily at every DOT encounter by the DOT worker.
Sputum smears and culture	• Obtain 3 sputa at the start of treatment and every 2 weeks until smear conversion, followed by 2-3 sputa every month until culture conversion, and then at least 1 sputum monthly throughout treatment.
Weight	• At start of treatment, weekly until stable, and then monthly throughout treatment.
Height	• At start of treatment for all (to be able to assess lean body weight or BMI); monthly for children (to assess growth).
Drug-susceptibility testing (DST)	At baseline for first- and second-line anti-TB drugs. (see Curry Survival Guide **Chapter 2, *Diagnosis*** pages 19-21 for more on testing for drug resistance). Repeat DSTs when: • Growth on a specimen collected >8 weeks into treatment, • Smear or culture reversion from negative to positive • Relapse
Chest radiograph	• At baseline, every 3 to 6 months during treatment, and at the end of treatment.

Source: Adapted from: Table 1: Curry Survival Guide (page 204)

Post-treatment Monitoring

- At the end of treatment, obtain a sputum specimen for AFB smear-and-culture and a plain chest radiograph.
- At 3-, 6-, 12-, 18- and 24-months post treatment, conduct the following:
    - TB symptom review
    - Medical evaluation
    - Sputum for AFB smear-and-culture (no NAAT as it can be falsely positive following treatment)
    - CXR

Drug Specific information

<table>
<tr><td rowspan="4">Bedaquiline (BDQ)</td><td></td><td>Weeks 1 – 2: 400 mg (4 tablets of 100 mg) given orally, once daily
If some of the 400 mg doses are missed during the 1st 2 weeks of treatment continue the loading doses until all 14 doses are completed before switching to the lower, 200 mg dose.
Weeks 3 – 26: 200 mg (2 tablets of 100 mg) three times per week, for a total dose of 600 mg per week</td></tr>
<tr><td>Interruption in Treatment</td><td>If 400 mg loading doses have been completed but there is a subsequent interruption in treatment, refer to this table for a possible reloading strategy.*
<table><tr><th>Duration of interruption</th><th>Reloading Strategy</th></tr><tr><td>< 2 weeks</td><td>No reloading needed</td></tr><tr><td>2 - 4 weeks</td><td>3 days 400 mg bedaquiline daily</td></tr><tr><td>1 - 12 months</td><td>7 days 400 mg bedaquiline daily</td></tr><tr><td>≥12 months</td><td>14 days 400 mg bedaquiline daily</td></tr></table></td></tr>
<tr><td>Therapeutic Drug Monitoring (TDM):</td><td>• Therapeutic drug monitoring at about 2 weeks after starting therapy, obtain levels at 5h and 24h after dose is given. (There is no consensus on the use of TDM for BDQ or pretomanid.)
• Draw 2 ml of serum for each collection.</td></tr>
<tr><td>Other Monitoring:</td><td>• EKG at baseline, 2-weeks, 4-weeks, and then monthly while on treatment. For individuals with risk factors for QTc prolongation check weekly for several weeks until stable then continue no less than monthly. Stop BDQ if QTc > 500 and monitor EKGs frequently until QTc returns to normal.
• Baseline potassium, calcium and magnesium, repeat if QTc prolongation occurs.
• Baseline and monthly ALT, AST, Alk phos and T. bilirubin.</td></tr>
<tr><td rowspan="2">Pretomanid</td><td></td><td>200 mg once daily for 26 weeks (200mg tablet)
*Note: no dose modifications allowed (adapted from NIX trial procedures and data)</td></tr>
<tr><td>Therapeutic Drug Monitoring (TDM):</td><td>• Therapeutic drug monitoring at about 2 weeks after starting therapy, obtain levels at 5h and 24h after the dose is given. (There is no consensus on the use of TDM for BDQ or pretomanid.)
• Draw 2 ml of serum for each collection.</td></tr>
</table>

	Other Monitoring:	• EKGs at baseline 2-weeks, 4-weeks, and then monthly while on treatment • Baseline electrolytes, repeat if QTc prolongation occurs. • Visual acuity at baseline and monthly. • Baseline and monthly CBC and liver profile. • Amylase and lipase if abdominal pain develops.
Linezolid (LZD)		600 mg daily for 26 weeks (600 mg tablet)
	Therapeutic Drug Monitoring (TDM):	TDM through University of Florida is available and typically is ordered after two weeks of treatment. Dosing may be reduced, temporarily interrupted, restarted at same or lower dose, or discontinued after the 1st month. See Curry Survival Guide TDM for linezolid pages 128-129 • Obtain therapeutic drug monitoring blood levels after 2 weeks of therapy. Obtain the levels just before the next dose is given (trough level) as well as levels at 2 hours and 6 hours after the dose is given- for a total of 3 blood draws in one day. ▪ identify who will follow this process along at the hospital lab and being in close communication ▪ Plan to meet patient at the lab for in-person DOT after the trough sample is drawn and to ensure blood levels are drawn on time. • Draw 2 ml of serum for each collection. ▪ WA State PH Lab (PHL) can do all the specimen processing if LHJ is unable to centrifuge the collection tubes if it gets to state PHL within an hour (although we have received collection tubes at two hours and still able to separate the serum). Once PHL has all three blood draws, they can plan for shipment to University of Florida after freezing the serum for shipment. ▪ For LHJs unable to use the PHL, see laboratory guidance provided in this document Sample Handling Instructions. • Use this form for submitting your specimens to University of Florida. Infectious disease pharmacokinetics lab requisition. Forms and Catalog » Infectious Disease Pharmacokinetics Laboratory » College of Pharmacy » University of Florida (ufl.edu) • University of Florida Pharmacokinetics Laboratory contact information • The results will come to the managing provider listed on the requisition. Please send a copy of results to TBServices@doh.wa.gov. • Once we obtain the organism's MIC for LZD, we can discuss whether it is appropriate to decrease the LZD to 600mg po TIW to minimize toxicity vs. maintaining the 600mg daily dose. Our goal is to get a level of linezolid that is 4-16x the MIC* and to maintain the trough level <2, a level that several studies have found is associated with low frequency of adverse effects. ***NOTE:** the NIX trial looked only at daily LZD 1200mg, but many patients had to stop LZD due to neurologic or hematologic toxicity. Several studies have indicated that risk of these toxicities is low if the trough level is <2.

	Other Monitoring:	• Monitor for peripheral and central neuropathy as well as optic neuritis with each dose. Neuropathies can be unusual, including loss of taste, hearing, numbness, pain or tingling among other things. Ensure staff is alert to this, hold TB meds if symptoms develop and ask physician for evaluation. • Monitor CBC weekly during the initial period, then monthly and as needed based on symptoms. • Screen monthly for visual acuity and color discrimination.

*****Source: Koele, S. E., van Beek, S. W., Maartens, G., Brust, J. C. M., & Svensson, E. M. (2022). Optimized Loading Dose Strategies for Bedaquiline When Restarting Interrupted Drug-Resistant Tuberculosis Treatment. *Antimicrobial agents and chemotherapy*, *66*(3), e0174921. https://doi.org/10.1128/AAC.01749-21

Monitoring Timeline and Checklist

Timing of labs, EKG, etc., patient will likely be seen weekly for the first month.

Baseline:

- ☐ CMP (including potassium and calcium)
- ☐ magnesium (order separately)
- ☐ CBC
- ☐ EKG
- ☐ HIV test
- ☐ TSH
- ☐ Hearing test
- ☐ Vestibular function/balance
- ☐ CXR (**And** every 3 to 6 months during treatment and at the end of treatment)
- ☐ Sputum every 1to 2 weeks
- ☐ Vital signs + weight
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Pregnancy test for people of childbearing age

1 week:

- ☐ Monitor CBC (for LZD) weekly during the initial period, then monthly and as needed.
- ☐ EKG (individuals with risk factors for QTc prolongation should be checked weekly until stable for several weeks, then no less than monthly)

2 weeks:

- ☐ CMP (for BDQ)
- ☐ CBC (for LZD)
- ☐ EKG (for BDQ)
- ☐ Therapeutic drug monitoring levels (for LZD, 24-hour trough, 2-hour post dose, 6-hour post dose)

3 weeks:

- ☐ Monitor CBC (for LZD) weekly during the initial period, then monthly and as needed

4 weeks (1 month):

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ Monthly sputum

8 weeks (2 months):

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ Monthly sputum

12 weeks (3 months):

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ Monthly sputum

16 weeks (4 months):

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ Monthly sputum

20 weeks (5 months):

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ Monthly sputum

24 weeks (6 months):

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ Monthly sputum

26 weeks/end of treatment:

- ☐ CMP
- ☐ CBC
- ☐ EKG (for BDQ)
- ☐ Vision (Snellen and Ishihara color test)
- ☐ Vital signs + weight + balance
- ☐ **CXR (important to get this one)**

Post treatment: Every 4 months in the first year and then every 6 months in the second year after treatment completion. Ask at the ***Longitudinal Case Consultation Panel*** meetings recommended monitoring and timing.

- ☐ CXR
- ☐ Vital signs + Weight
- ☐ Sputum
- ☐ Symptom Screen

Resources / Articles of interest

Guidance Documents

- Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. Updated 5/4/2023.
- Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd Edition (Entire Guide as well as by chapter) 10/2019.
- Curry International TB Center. Drug Resistant TB: A Survival Guide for Clinicians. Chapter 4. 3rd edition. 2022 Updates.
- Treatment of Drug-Resistant Tuberculosis An Official ATS/CDC/ETS/IDSA Clinical Practice Guideline 9/2019.
- NTCA Bedaquiline Access Guidance. WHO - catalogue of M.TB mutations and their association with drug resistance: Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014. 15, Management of contacts of MDR-TB patients.

Research Articles

- Implementation of BPaL in the US: Experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin intolerant TB Disease (Clinical Infectious Diseases) May 30, 2023
- Editorial Commentary: Bedaquline, Pretomanid and Linezolid (BPaL) for MDR-TB treatment in the US: a BIG deal (Clinical Infectious Disease) Journal Article - May 30, 2023
- A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. TB-PRACTECAL Study Collaborators. N Engl J Med; 387:2331-2343. December 22, 2022.
- Novel 6-Month Treatment for Drug-Resistant Tuberculosis, United States. Emerging Infectious Diseases, *27*(1), 332-334. Haley, C. A., Macias, P., Jasuja, S., Jones, B. A., Rowlinson, M., Jaimon, R....Goswami, N. D. (2021). Same article posted on CDC EID page
- Reduced dosing of linezolid in three-drug TB regimen lessens side effects. Findings from the 6-month ZeNix trial indicated that a three-drug regimen for highly resistant tuberculosis was safer and just as effective when it included reduced doses or shorter durations of linezolid, researchers reported.
- Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med 2022; 387:810-823 DOI: 10.1056/NEJMoa2119430 9/2022.
- Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D.

McHugh, Ph.D., Genevieve H. Wills, M.Sc., et al., for the Nix-TB Trial Team* March 5, 2020. N Engl J Med 2020; 382:893-902.

Services / Tools

- Link to University of Florida Therapeutic Drug Monitoring Forms: Forms and Catalog » Infectious Disease Pharmacokinetics Laboratory » College of Pharmacy » University of Florida (ufl.edu).
- Options for Obtaining Mobile Electrocardiogram (EKG), WA DOH.
- Guidance on requirements for QTc measurement in ECG monitoring when introducing new drugs and shorter regimens for the treatment of Multi/Extensively Drug-Resistant Tuberculosis (challengetb.org)
- Mayo QTc calculator - tool to calculate the QTc using results from an EKG or mobile EKG device
- For **TDM frequency** see the Infectious disease pharmacokinetics lab requisition form

Bedaquiline Resources:

NTCA webpage has detailed information on accessing Bedaquiline.

- NTCA Bedaquiline Access Guide
  - **List of Contacts** for Bedaquiline procurement see page 1
  - Johnson & Johnson Patient Assistance Foundation (JJPAF) program and JJPAF Application
  - Step by step details on how to fill out application form start on page 29

Therapeutic Drug Monitoring

University of Florida
idpl.pharmacy.ufl.edu
peloquinlab@cop.ufl.edu
352-273-6710

National Jewish Health
njlabs.org
willeyr@njhealth.org or clinreflabs@njhealth.org
303-398-1422

Contact for Assistance

- Washington State TB Program: 206-418-5500 or TBService@doh.wa.gov
- Washington TB Collaborative Network (WTCN):
  - Phone: 206-744-4579
  - Email: tb.wa@wtcnservices.com
  - Download the WTCN brochure to learn more.