NTP Clinical Protocol

For New Drugs (Bedaquiline & Delamanid) in Pakistan

Based on WHO Guidelines

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New treatments for drug-resistant tuberculosis (DR-TB) are urgently needed. Two new drugs, Bedaquiline and Delamanid, have recently been released, and several new drugs and treatment regimens are in the pipeline. Misuse of TB drugs is a principal cause of drug resistance. As new drugs and regimens reach the market, the need to make them available to patients must be balanced with regulation of their use so that resistance to the new drugs can be prevented.

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CHAPTER # 1: INTRODUCTION

1.1 Introduction:

Bedaquiline belongs to a new class of drugs called Diarylquinolines, and is indicated as part of combination therapy in adult patients (≥18 years) with pulmonary multidrug-resistant tuberculosis (MDR- TB). Bedaquiline is the first new drug developed specifically to treat TB in over 40 years.

Treatment success rates among patients with MDR-TB--especially those with resistance to second-line drugs--are poor, and the new drugs offer an opportunity to improve health and decrease transmission. In order to achieve the best possible outcomes, however, the drugs need to be given in a systematic fashion so optimal results are achieved for patients, providers, and the TB program.

Misuse of TB drugs is a principal cause of drug resistance. As new drugs and regimens reach the market, the need to make them available to patients must be balanced with regulation of their use so that resistance to the new drugs can be prevented" Data on BDQ show that when it is reserved for late use and only given to the "desperate" patients, outcomes are not as good as when it is used early, and restricting it actually leads to more resistance

WHO has recently changed the groupings of the drugs in their new guidelines. There is no more group 5(WHO 2016 guidelines). Rather there are Group A, B, C, and D and within group D there are D1 drugs (first line agents), D2 drugs (BDQ and DLM) and D3 drugs like PAS, Imipenemn. For more details please refer to DR TB Guidelines updated 2016. These protocols have been prepared in line with revised grouping of medicine.

Moreover, phase 111 trials to generate a more comprehensive evidence are still under process and will be helpful to inform future policy on bedaquiline. On the basis of phase 3 trials, WHO will review, revise, update the interim guidance based on use of BdQ in almost 5000 patients globally.

1.2   Programmatic considerations for introducing bedaquiline in the management of MDR-TB (WHO 2015)

NTP along with selected PMDT sites managing drug-resistant TB will have the following goals when introducing the use of bedaquiline.

- To provide early access to drugs to patients with limited treatment options.
- To limit the risk to the patient by monitoring for and managing adverse events
- Information on adverse effects monitoring and management for all patients on bedaquiline be kept track of through Active pharmacovigilance.

- To protect emergence of resistance to bedaquiline.
- To ensure that the highest standards of clinical ethical conduct and human rights are respected.

1.3   Summary of Key Facts about Bedaquiline:

✓ Strong bactericidal and sterilizing activity against *M. tuberculosis* organisms, specifically targeting mycobacterial adenosine triphosphate (ATP) synthase, an enzyme that is essential for the supply of energy to *Mycobacterium tuberculosis.*

✓ It has better absorption when the drug is taken with food versus when taken fasting

✓ Reported cross-resistance of bedaquiline with clofazimine. Although the clinical implications are not clear

✓ Bedaquiline has a slow terminal elimination profile, with a terminal half-life of approximately 5.5 months

✓ Limited experience with use of bedaquiline in children, pregnant women, extrapulmonary disease, and the elderly. Though there is now growing evidence that BdQ can be used in children over 12 years having 30 kg weight and also in extra pulmonary cases.

✓ There is minimal information on its use in HIV-infected patients, whether on antiretroviral treatment (ART) or not. In South Africa BdQ has been satisfactorily used in HIV infected patients.

✓ there was an observed risk of death, however, no evidence that directly linked the drug to the cause of death was however seen

✓ Use of Bedaquiline can cause QT prolongation, resulting in ventricular tachy - arrhythmias like torsades de pointes and a risk factor for sudden death. Moreover, concomitant use with other QT prolonging drugs may cause additive effect.

✓ Bedaquiline can also cause hepatotoxicity. Conditions and medications associated with hepatotoxicity could pose additional hepatotoxic risks.

✓ it is only given for the first 24 weeks of treatment along with WHO background regimen and total duration of treatment will remain same as per WHO definitions

✓ Drug susceptibility testing (DST) for bedaquiline has not yet been standardized

✓ Bedaquiline may play a crucial role to strengthen the regimen for many patients

✓ Bedaquiline should not be added alone to a failing regimen or in the middle of treatment, but can be added to replace the drug causing toxicity like, Injectable and Cycloserine.

1.4   Criteria of WHO 5 Conditions for use of Bedaquiline in Pakistan:

1.4.1   Effective treatment and monitoring:

A sound treatment monitoring system is already in place at all PMDT sites, however each eligible patient while enrolled on Bedaquiline containing regimen at selected

PMDT sites will be closely monitored for treatment response as per standard protocols mentioned in this document.

1.4.2   Proper patient inclusion:

Only patients will be enrolled those who meet the set inclusion and exclusion criteria mentioned in clinical protocols.

1.4.3   Informed consent:

The informed consent process must be documented and signed by the patient and is the essential condition for enrolment on BdQ. The due process for informed consent will be followed by ensuring that the patient is:

1.4.3.1   Aware of the novel nature of bedaquiline;

1.4.3.2   appreciates the reason why the drug is being proposed for inclusion in their treatment regimen;

1.4.3.3   Recognizes the possible benefits and potential harms associated with treatment

1.4.4   Adherence to the principles of designing a WHO-recommended MDR-TB regimen:

Bedaquiline is to be introduced alongside other anti-TB drugs in composing an effective second-line regimen based on WHO guidelines; the general composition/constructing the regimen and duration of MDR-TB treatment remains the same. It should be noted

When an effective, and reasonably well-tolerated MDR-TB regimen can be composed with conventional second-line drugs, bedaquiline is not necessary (WHO interim policy guidelines 2015)

1.4.5   Active pharmacovigilance and management of adverse events:

Active pharmacovigilance measures are already in place at PMDT sites to ensure early detection and proper management of side effects. However, patients with Bedaquiline containing regimens a robust pharmacovigilance system will be in place to record minor to sever adverse event or reaction. The general principle is to monitor potential adverse events closely and manage them as quickly and effectively as possible. For this purpose NTP provided sheets/tools on pharmacovigilance will be used .

CHAPTER # 2: ABSOLUTE CONTRA INDICATIONS, RELATIVE CONTRA INDICATIONS AND CAUTIONS

For absolute contraindications Bdq cannot be used

For Relative contraindication, bedaquiline should be avoided but could be used in situations where the options of treatment are extremely limited and the benefit of bedaquiline outweighs the potential risks

For Cautions: BdQ can be used but with additional care and monitoring

2.1   Absolute Contra- indications:

Following are the examples of absolute contraindications;

Patient refuses to consent: The patient decides to not to accept the medication after being properly counseled and informed about the benefits and risks associated with the use of bedaquiline.

Hypersensitivity: In case of hypersensitivity to any of the substance or excipients of the formulation

High risk for cardiac complications. At baseline ECG , patient has a QT interval greater than 500 ms, history of torsades de pointes (TdP) or cardiac ventricular arrhythmias or severe coronary artery disease.

2.2   Relative contraindications:

In the following situations BdQ should be avoided, but can be used on case by case based on consultation outweighing the risks and benefits, when effective treatment cannot be constructed;

Children or persons under 18 years of age. BdQ use in this group should be avoided until further data/recommendations are available, but can be used in children over 12 years weighing 30 kg if benefit overweighs harm and decided in review panel. .

Pregnancy: So far recommendations are not to use BdQ in pregnancy until further evidence is available.

Breast Feeding: This is still not sure that bedaquiline and its metabolites are passed into human breast milk, however, may be used in case by case situations where its use outweighs the benefit. Moreover, the decision should also be made that breastfeeding should be continued or discontinued in nursing mothers.

2.3   Cautions:

- **Use of BdQ in the Children & Elderly:** Because of not having sound evidence of safety of use in elderly >65 years and children < 18 years, the use of BdQ should be with special care/caution and proper clinical judgment. But inclusion of adults >65 to 68 years can be considered on case by case basis.
- **Renal Impairment:** The evidence of use of BdQ is scarce in patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis. Therefore, in this group of patients BdQ should be used only if benefit outweighs risks. However, in patients with mild or moderate renal impairment dose adjustment of BdQ is not required.
- **Hepatic Impairment:** As above, in patients with mild or moderate haptic impairment dose adjustment of BdQ is not required.
- **Deranged Serum Potassium:** potassium levels should be corrected before starting bedaquiline and carefully monitored as hypokalemia is associated with QT prolongation and also risk of arrhythmias due to hypo or hyperkalemia. Therefore ECG should be carefully observed before starting treatment with BdQ.
- **Extra pulmonary disease only:** BdQ can be used in such patients and inclusion may be
- Considered when potential benefit outweighs the risk.
- **Co-administration with QT-prolonging drugs.** Following drugs may have impact on QT prolongation when co-prescribed with BdQ. Therefore, if prescribed more frequent monitoring is required with ECG throughout treatment period;
- Haloperidol/haldol and also amitriptyline/tricyclic antidepressants.

- Moxifloxacin (to a lesser extent with levofloxacin), Clofazimine, Macrolide drugs (erythromycin, clarithromycin, azithromycin), Serotonin 5-HT3 receptor antagonist i.e. anti-nausea drugs commonly used in MDR-TB **Dolasetron, Ondansetron**
- Azole antifungal agents (e.g., ketonazole, itraconzaole, fluconazole), Some antimalarials (quinine sulfate, chloroquine), drugs used for psychiatric disorder (e.g. chlorpromazine, haloperidol, thioridazine)
- For this purpose a patient card will be prepared with information of all drugs for caution. This card will be presented to any doctor by the patient while seeking treatment for any problem during ambulatory care.

Concurrent use of bedaquiline with other group D2 drug(Delaminid)anti-TB drugs:

So far Delamanid is not available in Pakistan, however simultaneous use with BdQ in is not recommended by WHO. But growing evidence in other countries shows that concomitant use of BdQ and Dlm is safe.

CHAPTER # 3: TREATMENT OF BEDAQUILINE (BdQ) WITH WHO BACKGROUND REGIMEN

3.1: Inclusion & Exclusion Criteria for BdQ

3.1.1   Inclusion Criteria

- Confirmed RR,MDR, pre-XDR* and XDR-TB patients
- where four essential drugs cannot be ensured in the treatment selection
- MDR TB patients with previous exposure of FQ & Am/Km/Cm for > 1 month and results of repeat DST is not available.
- Patients with two or more group C drugs compromised (Eto,Cs,Cfz,Lzd)
- Intolerance to one of the SLDs
- Close contacts of patients where index case has resistance to either FQ, Km/Am/Cm or XDR TB
- Failure of standard MDR TB treatment as per WHO 2013 definition
- Long standing MDR TB cases with extensive bilateral lung damage or advanced disease
- MDR TB patients on treatment with hearing impairment proven by audiometry
- Pulmonary disease only
- Age ≥ 18 years and under 65 years, over 12 years weighing 30 kg or above and up to 68 years can be considered when potential benefit outweighs the risk based on decision in review panel.
- HIV co-morbid conditions
- Written Informed consent
- Patients where close monitoring can be ensured and willing to reside in the catchment area of selected PMDT sites

3.1.2   Exclusion Criteria

- Age less than 18 and more than 65 Years ,exceptions can be made as above
- Pregnancy
- Evidence/history of cardiac disease/event at baseline
- A confirmed prolongation of QTc interval(Fridercia formula) a demonstration of QTcF(Fridercia correction) interval > 500 ms, pathological Q waves in the screening ECG
- Risk factors for TdP(e.g heart failure ,hypokalemia, hypomagnesemia) if cannot be corrected
- Severe Hepatic disorder
- Any patients where close monitoring cannot be ensured

- Any patient for whom the address cannot be verified
- Not willing to provide informed consent

*Note: Pre-XDR is not an official term and describes patients with FQ or Inj resistance

3.2 Diagnostic Procedures

Most of the patients who will be commenced on BdQ containing regimen will already either be confirmed pre-XDR, XDR or failures of MDR-TB treatment. However, as per NTP protocols following diagnostic and DST methods will be used. Culture /DST will be requested as per existing NTP protocols, but with good practices of sample packing and transportation to avoid contamination.

- Smear microscopy
- G.Xpert for detection of Rifampicin resistance
- LPA 1st line to detect resistance to H and R
- LPA 2nd line for rapid molecular DST to FQs and Injectable
- DST to 1st and 2nd line drugs through LJ/MGIT
- Other investigations as per Table 3.6

3.3: Duration of Treatment

The overall duration of treatment of MDR-TB will remain as per National DR-TB guidelines 2015 while treating patients with BdQ (minimum 20 months for MDR and 24 months for pre-XDR and XDR-TB, with minimum 8 months of injectable).

Table 1: Length of treatment of bedaquiline-containing regimens

Drug	Suggested Duration(months)	Comments
Bedaquiline	6	BdQ should be added to WHO back ground regimen
Injectable Drugs	8	minimum duration of 8 months as per national policy
Other oral Anti TB drugs in the regimen	20 months	Minimum duration of 20 months as per national policy. For pre XD and XDR-TB cases, minimum duration will be 24 months

3.4: Dosing Of Bedaquilne:

According to WHO guidelines Bedaquiline should only be given for six months (24 weeks)

Currently BdQ is provided in 100 mg tablets and following is the dosage as per WHO standard recommendations:

- Week 1–2: Bedaquiline 400 mg (4 tablets of 100 mg) daily (seven days per week).
- Week 3–24: Bedaquiline 200 mg (2 tablets of 100 mg), three times per week (with at least 48 hours between doses) for a total dose of 600 mg per week.
- Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only.
- Bedaquiline is not advised to be continued after completion of six months(24 weeks)
- Bedaquiline should not be added in the middle of the treatment or in failing regimen
- If there is indication of BdQ a new regimen should be constructed as per guidelines available in clinical protocols
- Bedaquiline can be taken concomitantly with other anti-TB drugs
- This drug should be advised with light meal ,as it has good absorption when taken with food
- Dose adjustment is not required under any specific condition, even if associated agents are known to affect bedaquiline bioavailability. In such condition WHO has advised to monitor potential adverse events closely and manage them as quickly and effectively as Possible.

3.5: Missed Doses of Bedaquiline & Management:

First two weeks of Treatment: During this period if a dose is missed, patient should continue the treatment and should not make up for the missed dose.
From Three weeks and onward: In case if a 200 mg dose is missed, patient should be advised to take the missed dose as early as possible and continue the three time/week regimen .

3.6: Table: Resistance patterns & constructing the Bedaquiline Containing Regimen

S #	Scenario	Suggested Regimen	Comments
1	Patient with RR/MDR TB, DST after 8-10 weeks shows only any of the FQ resistance	8Z,Am,Lfx(MfX),Eto,Cs,Lzd,Cfz, BdQ(6),/16Z,Lfx(MfX),Eto,Cs,Lzd,Cfz	- If Ofx is resistant, use Lfx unless its efficacy is compromised because of previous use in failing regimen and H/O close contact with a patient resistant to FQ. - If LfX is resistant/previous exposure in failing regimen/known contact with LfX resistant, the use of MfX should be considered. - If Mfx resistant is reported or previous exposure in failing regimen, H/O close contact with MfX resistant, LfX should be considered instead - Lfx has lower overlapping toxicity with

			BdQ as compare to Mfx, - Combined use of BdQ, MfX and Cfz should be avoided due to increased risk of QT prolongation - As BdQ has long half-life(6 months) so, addition of MfX to the regimen ,if BdQ is stopped may result in cardiac toxicity If there is exposure to SLDs >30 days, then drugs from group 5 should be added as per National DR TB guidelines - High dose INH may be considered, if reported susceptible or DST shows low level resistance.
2	Patient with RR/MDR TB with any of the FQ resistance at the time of enrolment (patient came with reliable DST or when LPA 2nd line available)	8Z,Am,Lfx(MfX),Eto,Cs,BdQ(6)/16Z,Lfx(MfX),Eto,Cs	- If Ofx is resistant, use Lfx unless its efficacy is compromised because of previous use in failing regimen and H/O close contact with a patient resistant to FQ. - If LfX is resistant/previous exposure in failing regimen/known contact with LfX resistant, the use of MfX should be considered. - If Mfx resistant is reported or previous exposure in failing regimen, H/O close contact with MfX resistant, LfX should be considered instead - Lfx has lower overlapping toxicity with BdQ as compare to Mfx, - Combined use of BdQ, MfX and Cfz should be avoided due to increased risk of QT prolongation - As BdQ has long half-life(6 months) so, addition of MfX to the regimen ,if BdQ is stopped may result in cardiac toxicity - If there is exposure to SLDs >30 days, then drugs from group D3 should be added as per National DR TB guidelines
3	MDR TB Patient with resistant to one of the Injectables, and susceptibility to FQs	8Z,Am/Cm,Lfx(MfX),Eto,Cs,BdQ(6)/16Z,Lfx(MfX),Eto,Cs	- If DST suggests resistant to Am or previously used, then prescribing Cm is advised and vice versa - if there is resistant to all injectable drugs, then WHO has advised not to use Injectable drugs - Prefer using Lfx instead of Mfx when using BdQ - Group D3 drugs other than BdQ may also be added if criteria of addition of these drug is suggestive as per DR TB National guidelines
4	MDR TB patient having resistant	8Z,Am,Lfx(MfX),Eto,Cs,Lzd,BdQ(6)/12Z,Lfx(MfX),Eto,Cs,Lzd	If resistant to Eto & Cs together is documented BdQ should be added to the

	to 2(two) or more group C drugs(Eto,Cs,Lzd,Cfz)		regimen • Eto,Cs can be added to the regimen but should not be counted as clean drug • If there is no confidence on any of the group C drugs, add drugs from group D 3 • If there is confidence on only one group C drug, two group D3 drugs should be added • In cases where confidence is on two group C drugs, one drug from group D 3 should be added • In some programs, ETO, CS is not included in regimen if reported resistant and BdQ is given instead.
5	XDR-TB (MDR + resistant to one of the Injectable and one of the FQs	12Z,Cm,Lfx(MfX),Eto,Cs,Lzd,Cfz,BdQ(6),/12Z,Lfx(MfX),Eto,Cs,Lzd,CfZ	• If DST result shows susceptibility to one of the injectables AM/Km or Cm, then susceptible one should be added to the regimen • Where there is resistance to all injectable, in such cases WHO has advised not to consider addition of Injectable to the regimen • However, if patient has not exposed to one of the injectable in the past, that may be used • If Ofx is resistant, use Lfx unless its efficacy is compromised because of previous use in failing regimen and H/O close contact with a patient resistant to FQ. • If LfX is resistant/previous exposure in failing regimen/known contact with LfX resistant, the use of MfX should be considered. • If Mfx resistant is reported or previous exposure in failing regimen, H/O close contact with MfX resistant, LfX should be considered instead • Lfx has lower overlapping toxicity with BdQ as compare to Mfx, • Combined use of BdQ, MfX and Cfz should be avoided due to increased risk of QT prolongation • As BdQ has long half-life(6 months) so, addition of MfX to the regimen ,if BdQ is stopped still may result in cardiac toxicity • If there is exposure to SLDs >30 days, then drugs from group D2 and D3 should be added as per National DR TB guidelines.

6	TB patient Rif resistant with H/O close contact with MDR TB patient having resistant pattern of FQ	8Z,Am,Lfx(MfX),Eto,Cs,BdQ(6)/16Z,Lfx(MfX),Eto,Cs	• Please follow same protocols as mentioned in S# 1 above
7	A TB case RR reported with H/O close contact of XDR-TB	12Z,Am/Cm,Lfx(MfX),Eto,Cs,Lzd,Cfz, BdQ(6)/12Z,Lfx(MfX),Eto,Cs,Lzd,Cfz	• DST to 1st and 2nd Line drugs should be requested at baseline • Please follow instructions as mentioned in S # 4
8	MDR TB Treatment Failure	8Z,Am/Cm,Lfx(MfX),Eto,Cs,Lzd,Cfz,BdQ(6),PAS,Amx/Clv/16 Z,Lfx(MfX),Eto,Cs,,Lzd,Cfz, PASAmx/Clv	• DST to SLDs should be requested • The combined use of Mfx, Bdq and CfZ should be avoided, if used then frequent and strict monitoring through ECG is required due to increased risk of QT prolongation • In case of exposure to AM, Cm should be used • High dose INH 16-12 mg/kg may be used if DST results show susceptibility or low level resistance • Group C, D1, D2 and D3, should be used as per NTP guidelines
9	Intolerance to one of the SLDs (for example Inectables or Cs)	8Z,Lfx(MfX),Eto,Cs,BdQ(6)/16 Z,Lfx(MfX),Eto,Cs,	• If patient has progressive ototoxicity or renal toxicity, Inj can be replaced with BdQ • Likwise if patient is not tolerent to CS and develops psychosis, CS can be switched with BdQ • At the time of BdQ introduction it is important to assess the patient response to treatment as BdQ alone should not be added in failing regimen

3.7: Anti-Retroviral Regimen Options for Patients on Bedaquiline Therapy (Adopted from WHO 2015 DR TB guidelines)

Given the limited data on drug–drug interactions of antiretroviral with Bedaquiline, the following options for ART regimens can be considered:

• Two NRTIs with nevirapine [e.g. AZT-3TC (or FTC)-NVP]
• A NtRTI, a NRTI with nevirapine [e.g. TDF-3TC-(or FTC)-NVP]Review
• Triple NRTI (e.g. AZT-3TC (or FTC)-ABC)*

General recommendations

• Avoid efavirenz containing regimens
• Avoid regimens with protease inhibitors

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- More frequent monitoring of QT interval prolongation (every month with ECG)
- Be aware of potential additive liver toxicity with NVP and Bdq.

If the bedaquiline is stopped in a patient on ART because of QT prolongation, the ART is often continued except if dangerous arrhythmias are present, then all QT-prolonging drugs are stopped.

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NRTI = nucleoside reverse-transcriptase inhibitor

NtRTI = nucleotide reverse-transcriptase inhibitor

3TC = lamivudine; AZT = zidovudine; NVP = nevirapine; FTC = emtricitabine; TDF = tenofovir

* Limited evidence on triple NRTI regimens (AZT-3TC/FTC-ABC) are associated with a lower ability to obtain good viral suppression and should only be used when other options are not possible

3.8:   Drug-Drug Interactions with Bedaquiline

The use of strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided while on bedaquiline, unless the benefit of treatment with the drug combination outweighs the risk. The examples of strong CYP3A4 inhibitors are Azole anti-fungal agents like ketonazole, itraconzaole, fluconazole

Additive or synergistic QT prolongation was observed when bedaquiline was co-administered with other drugs that prolong the QT interval. Following are some of the common drugs that can prolong the QT interval and care should be taken before prescribing these drugs with BdQ:

- Some medicines to treat a psychiatric disorder (e.g. chlorpromazine, haloperidol, thioridazine).

- Amitriptyline, Trycyclic antidepressants
- Antarrythamic drugs like procainamide, Disopyramide, Amiodranoe ,Sotalol
- Moxifloxacin, (levofloxacin to a lesser degree).
- Clofazimine ,though clinically not well established
- Macrolide antibacterial drugs (erythromycin, clarithromycin, azithromycin).
- Serotonin 5-HT3 receptor antagonist (like ondansetron, an anti-nausea drug commonly used in MDR-TB).
- Azole antifungal agents (e.g., ketonazole, itraconzaole, fluconazole).
- ARVs. The common three drug combinations used in ART can result in QT prolongation (Efavirenz, Protease Inhibitors and Ritonavir while NVP with BdQ can increase risk of hepatotoxicity)
- Some antimalarials (quinine sulfate, chloroquine).

If possible, avoid the use of QT-prolonging drugs with bedaquiline. If it is absolutely necessary to include a QT-prolonging drug, increase ECG monitoring as per protocols

Drugs that lower electrolytes (i.e. injectable agents used in TB/MDR TB) can result in a higher potential for arrhythmias (including sudden death) due to QT prolongation.

CHAPTER # 4: MONITORING AND MANAGING PATIENTS ON BEDAQUILINE THERAPY

Except BdQ all drugs in the treatment regimen constructed are those being used already in standard MDR TB treatment at PMDT sites in Pakistan. All side effects related to 1st to 5th group of MDR TB treatment should be identified early and managed properly. While BdQ has some additional potential side effects that include Cardiotoxicity, hepatotoxicity (could be common and severe. Experiences from other countries shared show that QTc prolongation may be seen in as many as 25% of patients, but only about 6% will have Qtc longer than 500msec. In terms of hepatotoxicity, there are not very many cases of fulminant or grade 3 or 4 hepatic events.

Hemoptysis and pancreatitis (could be rare). Therefore following is suggested for close monitoring of minor to major side effects recognition and management.

- Patients receiving bedaquiline should be clinically monitored closely throughout their treatment.
- PMDT sites should provide the facility of free of cost baseline and monitoring tests as per NTP guidelines. Moreover ancillary drugs prescribed for adverse effects should be free of charge or at the lowest possible cost if not available at hospital.
- Two other less commonly observed but possibly severe adverse effects (QT interval prolongation and hepatotoxicity) related to bedaquiline use in clinical trials need special attention for screening and management aspects.

- The most frequent and common adverse drug reactions (>10% of patients) during treatment with bedaquiline in the controlled trials were nausea, arthralgia and headache.
- The management of these side effects should be as per NTP guidelines

QT prolongation can result in ventricular arrhythmias (torsade de pointes) and result in death, and it is imperative that ECG measurements are taken before treatment with bedaquiline is started, and regularly during bedaquiline use. The QT interval must be corrected for the heart rate (adjustment is referred to as QT-corrected or QTc). The

Fredericia correction method (QTcF) is preferred. QT interval monitoring should be done. NTP will try to provide ECG machines that directly report the QTc interval.

Following are important notes on QT interval monitoring:

- The QT interval must always be corrected for heart rate.
- A value of greater than 450/470 ms is considered prolonged in male/female patients. If a male/female patient taking bedaquiline has a QTcF value of greater than 450/470 ms (or an increase of greater than 60 ms from baseline) on his or her ECG, electrolyte testing and more frequent ECG monitoring should be performed. A QTcF interval of

more than 500 ms is considered dangerous and is reason to stop the use of bedaquiline and all other QT prolonging drugs in the regimen, if QT interval does not correct with other measures
- Low or high serum electrolyte concentrations in the presence of a QT interval prolongation predisposes to arrhythmias.

Box below describes how the correction can be calculated using measurements on a graduated ECG rhythm strip.

BOX A: QTC Interval definition and Correction Formula (Adopted from WHO 2015 guidelines)

■ The QT interval in an ECG is measured from the start of the Q wave to the end of the T wave (see diagram below).
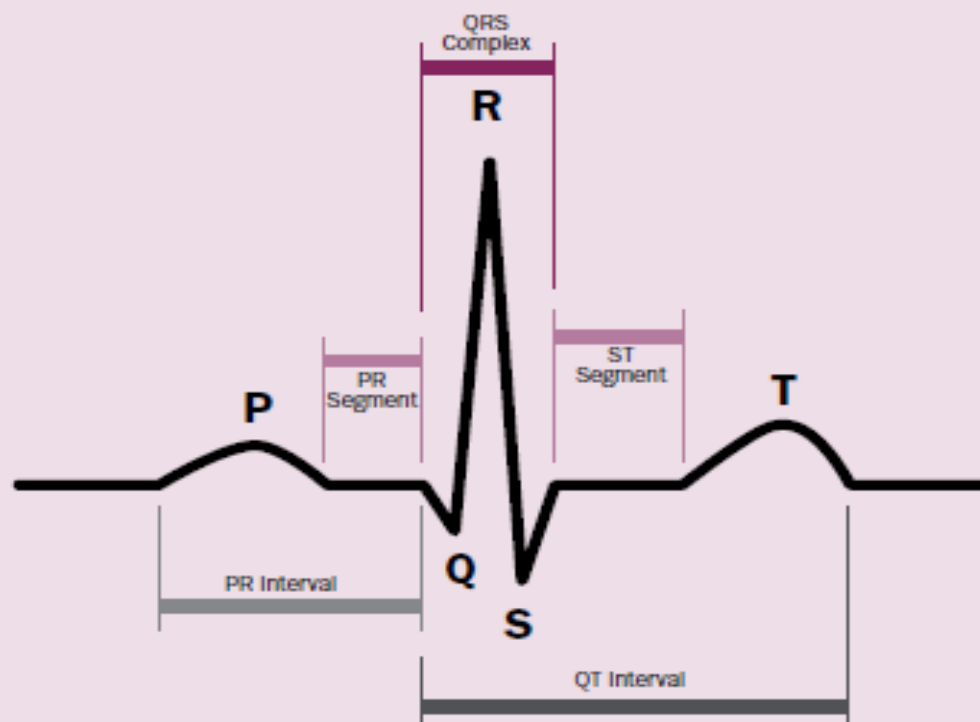
■ When monitoring the effect of bedaquiline, the QT interval needs to be adjusted (corrected) for the heart rate. Many ECG machines today provide an output of the corrected QT interval (QTc) automatically. If you are using a machine that does not, the following instructions can help you make the necessary correction.

· The preferred way to calculate the QTc is the Fredericia method (QTcF), which is derived by dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR) read from the ECG strip:

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

■ Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

■ A normal value for the corrected QTcF interval is equal to or less than 0.45 seconds (450 ms) in males or 0.47 seconds (470 ms) in females.

One large 5 mm × 5 mm box represents 0.2 seconds (200 ms) time and 0.5 mV amplitude.

1 mV (10 mm high) reference pulse

One small 1 mm × 1 mm block represents 40 ms time and 0.1 mV amplitude.

Amplitude

Time
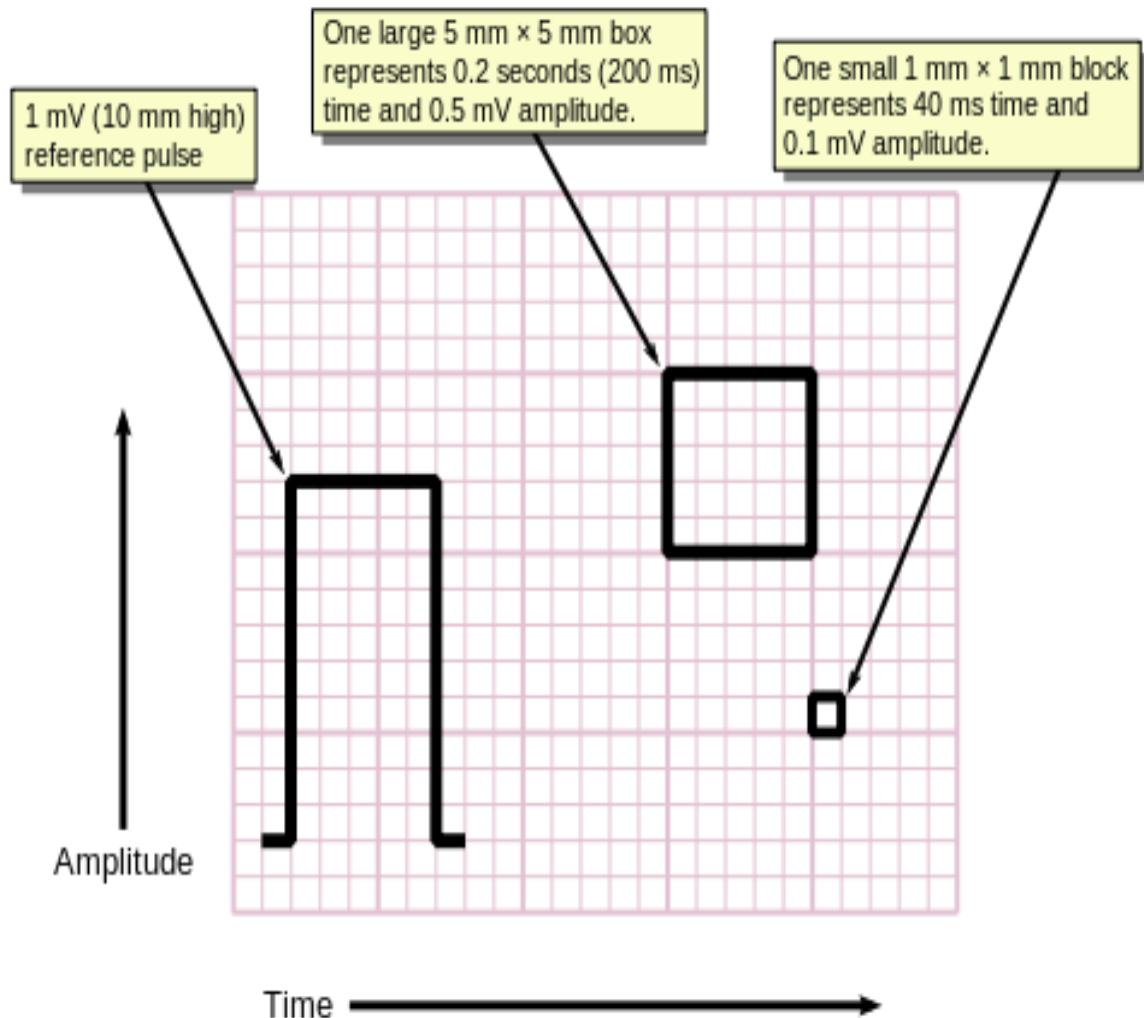
4.2: Frequency of QT Interval monitoring and management of QT Interval prolongation

An ECG should be obtained before initiation of treatment, and at least two, 2, 4, 8, 12 and 24 weeks after starting treatment with bedaquiline. Monitoring ECGs should be done monthly if other QT-prolonging drugs are included in the regimen).

Serum potassium (K+), ionized calcium (Ca++) and magnesium (Mg++) levels should be obtained at baseline and corrected if abnormal. Every effort should be made to have accurate testing for electrolytes. K+, Mg++ and ionized Ca++ should be monitored monthly while on bedaquiline. An abnormal value for electrolytes should be corrected. Most commonly, low values are due to second line anti-TB injectable drugs.

Whenever low potassium is detected, urgent management should be initiated with replacement and frequent repeat potassium testing (often daily) to document that the potassium is moving in the correct direction. If potassium is low, always check magnesium and calcium and replace as needed (If unable to check, strongly consider oral empiric replacement doses of magnesium and calcium).

Be aware that in patients who are critically ill, low calcium levels can be simply due to hypoalbuminaemia, which has no clinical significance because the active fraction (ionized) is not affected. However, to prevent missing a second hypocalcaemic disorder, measure the ionized calcium level whenever the albumin level is low.

Whenever **significant QTcF prolongation** is detected (absolute value >450 ms in males or >470 ms in females, or an increase of > 60 ms from baseline):

- Repeat ECG to confirm prolongation.
- Check K+, Mg++ and ionized Ca++ and correct levels if found to be abnormal.
- Withhold bedaquiline and injectable agent (if patient is still using) until the electrolytes have normalized.
- If the QTcF interval remains above normal value but still below 500 ms (and the patient is stable and electrolyte values are within normal limits) repeat weekly ECGs to confirm that QTcF interval is stable.

If the QTc interval is >500 ms (confirmed by repeat ECG) discontinue bedaquiline and all other QT-prolonging drugs in the regimen. However, since BDQ has such a long half-life. So stop the FQ first and see what happens. Then stop CfZ and see what happens, if the QTc is still prolonged, stop BDQ. But if the patient has symptoms, such as tachycardia, syncope, palpitations, weakness or dizziness, then stop BdQ right away.

-
- If the QTcF interval remains above normal value but still below 500 ms (and the patient is stable and electrolyte values are within normal limits) repeat weekly ECGs to confirm that QTcF interval is stable.
-
- Bedaquiline and all other QT-prolonging drugs are to be discontinued if the patient develops clinically significant ventricular arrhythmia. If bedaquiline is stopped to deter QT prolongation, monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline as BdQ has long half-life.
- If cardiac symptoms appear (tachycardia, syncope, palpitations, weakness or dizziness), obtain an ECG to check the QT interval and rule out an arrhythmia.
- Because of the long half-life of bedaquiline, if the ECG has QT prolongation at week 24, ongoing weekly monitoring should take place until the QT interval normalizes (even though the drug is no longer being given)

4.3: Liver function monitoring and Management of Hepatotoxicity:

- One of the major side effect of BdQ is liver toxicity, therefore enzymes should be monitored monthly.
- Preferably avoid prescribing hepatotoxic drugs while patient is on bedaquiline, especially patients with chronic hepatitis or cirrhosis

> **NOTE:**
> If aminotransferase (AST) elevations are accompanied by total bilirubin elevation >2x upper limit of normal (ULN), or aminotransferase elevations are >5x the upper limit of normal, bedaquiline needs to be discontinued

- Monitor symptoms and laboratory tests (alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin) at baseline, monthly while on treatment, and thereafter as needed.
- An increase in serum aminotransferases to >3x upper limit of the normal should be followed by repeat testing within 48 hours. Testing for viral hepatitis should be performed and other hepatotoxic medications reviewed and be considered for discontinuation.
- Evidence of new or worsening liver dysfunction (including clinically significant elevation of aminotransferases and/or bilirubin and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on bedaquiline should prompt additional evaluation

4.3.1: Conditions for Discontinuation of BdQ.

Aminotransferase elevations are accompanied by total bilirubin elevation >2 times the upper limit of normal;

Aminotransferase elevations are >5 times the upper limit of normal. , Many other agents can cause LFTs to be > 5x the ULN. Because of the long half life of BdQ, try stopping other drugs first

-
- Aminotransferase elevations persist beyond two weeks;
- Consider other anti-TB drugs (i.e. isoniazid, rifampicin/, pyrazinamide, ethionamide or PAS) as causative drug. If another drug is identified as the likely cause of drug hepatitis, consider re-challenging with bedaquiline.

4.4: Monitoring of Chest Pain and Hemoptysis

One of the clinical trial with BdQ reported frequently chest pain and hemoptysis. Therefore, patients presenting with hemoptysis or chest pain should be clinically investigated, including chest radiograph, pulse oximetry and ECG.

4.5: Monitoring of Pancreatitis

- Clinical trials that used bedaquiline versus placebo did not report pancreatitis very commonly. However, increase in pancreatic enzymes have been observed in patients taking bedaquiline, although it was rare and direct link with BdQ was not established. If signs & symptoms of pancreatitis (Upper abdominal pain that radiates into the back; it may be aggravated by eating, especially foods high in fat, swollen and tender abdomen, nausea and vomiting, fever, Increased heart rate) then request Lipase /Amylase and repeat if necessary.

4.6: NTP Task Force and Technical Working Group

- A Task Force consisting of key stakeholders from MDR TB unit, NRL, Research Unit and M&E unit will be established at NTP. This task force meetings will be held as necessary preferably on monthly basis for ist quarter and then in each quarter to oversee and discuss the process of BdQ introduction , outcomes and barriers.
- While Technical Working group has already been established at NTP involving stakeholders from MoH, partner organizations and Pakistan Chest Society. The approval from MoH has been received on the recommendations of 1st TWG meeting. Moreover, a 2nd meeting was also held where BdQ implementation plan was thoroughly discussed along with selection of pilot PMDT sites ,agreed and approved by MOH.
- The TWG meetings will be held twice a year to discuss the progress ON BdQ Introduction.

CHAPTER # 5: SIDE EFFECT MONITORING, RECORDING AND REPORTING

Where it is crucial to timely identify and manage side effects, at the same time it is also important to record and report all minor to major side effects. Above all that it is also necessary to do pre enrolment screening tests/investigations and also during follow up as suggested in below table.

5.1: Table: Monitoring and Evaluation Testing During DR TB Treatment with BdQ

Health Education & Counseling	At the time of enrolment and on each/monthly follow up
Clinical monitoring (essential requirements)	ECG, electrolytes, hepatic function tests.
Clinical Evaluation & weight	On each visit whatever the frequency is
Smear Microscopy	Monthly
Culture	Monthly during intensive phase, then every other month during continuation phase or as decided by the DR TB physician
DST	At baseline, then for patients who remain culture positive at month 4-6 or if reverted to positive culture any time during continuation phase
Chest Radiograph	Baseline ,then every 3-6 months or earlier as decided by DR TB physician
ECG	Before initiation of treatment, and at least at 2, 4, 8, 12 and 24 weeks after starting treatment. ECGs should be done at least monthly if other drugs that prolong the QT interval are included in the regimen. Given the long half-life of bedaquiline (5.5 months), one or more ECGs should be done after 24 weeks, based on clinical judgment
CBC	At baseline or later if indicated
S. Creatinine	Baseline then monthly while patient is on injectables ,specially for patients who have diabetes or renal disease
Electrolytes	Serum potassium should be obtained at baseline, if low calcium, and magnesium should be requested and corrected if abnormal before use of the drug. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected.
TSH	At baseline then every 3-6 months, especially when patient is taking Eto/Pto and PAS together. Monitor for signs and symptoms of hypothyroidism regularly.
Liver Enzymes	Monitor symptoms and laboratory tests (ALT, AST, and bilirubin) at baseline, monthly while on treatment, and thereafter as needed
Albumin	No specific precautions if Albumin is low check calcium

HIV	At baseline and repeat if indicated
Pregnancy Test	Initially for every female patient of child bearing age, then repeat if indicated. Family planning during treatment is important
Audiometry	Monthly during intensive phase, periodically afterwards
Visual Test	At baseline and Monthly if on E or on Lzd, otherwise use visual testing charts monthly , refer to ophthalmologist where indicated
DOT & Treatment supporter assessment	DOT, once daily for 2 weeks, thereafter 3 times per week, for 6 months. Other drugs in the MDRTB regimen require daily DOT throughout. Ensure that DOT provider is taking care of all aspects of daily DOT and assess the effectiveness and suitability of DOT provider/treatment supporter

5.2: Identifying Side Effects

- The introduction of BdQ is based on ambulatory model of care as in standard MDR TB treatment. However, MDR TB physician during review panel meeting should decide that patient being enrolled on BdQ containing regimen should be retained indoor for a specific period depending upon condition.
- However, each patient after given 1st dose of BdQ at MDR TB unit must be retained for 6-8 hours under close observation to monitor any severe side effects related to BdQ As nausea may happen and also this may be helpful I developing confidence of patient. This decision depends upon judgment of MDR TB physician and review panel. Recent experience from IRD (interactive Research and Development) project- Karachi has shown no such incident while patients enrolled on BdQ. But the number of patients is small hence utmost care must be observed
- At the time of health education/counseling session patient and treatment supporter/family member will be educated on cardiac signs and symptom like tachycardia, syncope, palpitations, weakness or dizziness. Also about liver toxicity symptoms such as fatigue, anorexia, nausea, jaundice, dark urine etc.
- Patient will be /counseled, advised that this is his responsibility to report the above mentioned signs/symptoms or any other if occur as early as possible to the treatment coordinator of PMDT site on the provided phone number.
- MDR TB physician/treatment coordinator should make sure that patient and treatment supporter fully understood that in case of any major side effect or problem while on ambulatory care he/she should reach to nearest emergency care hospital/facility with treatment card provided.
- Once the major complaint/event has been managed at emergency he/she should visit the PMDT site for any adjustments in treatment

5.3: Recording & Reporting of Side Effects/Events

As per WHO guidelines all side effects/adverse events should be recorded regardless of frequency and nature of event.

Whenever any minor to major side effect is detected or reported to MDR TB physician/treatment coordinator, this should be recorded on the already provided performa in DR TB register.

Each adverse event should be reported to pharmacovigilance monitoring committee

Establishment of pharmacovigilance committee is mandatory at PMDT site and provincial level, involving federal MDR Tb unit.

5.4: Pharmacovigilance committee:

Following is proposed Pharamcovigillance committee

5.4.1 PMDT site level:
   MDR TB physician, PMDT pharmacist, focal person MDR TB PMDT site. In charge of the committee will be HoD of pulmonology, who will oversee and monitor the committee.

5.4.2 Provincial level:
   • Provincial MDR TB Coordinator
   • Provincial pharmacist

5.4.3 Federal Level:
   • National Advisor MDR TB
   • Focal person BDQ intervention
   • Data Officer MDR TB
   • Pharmacist/DMU

5.5: Mechanism of Action of Pharmacovigilance committee:

The end point of mechanism of pharmacovigilance committee is to timely manage the identified/reported side effects. The committee will be responsible that all SOPs are being followed accordingly. The PMDT team is responsible for appropriate screening and close liaison with cardiology, gastroenterology and other departments so that adverse events can be managed properly.

Following is the flow of reporting of adverse events;

   • Each adverse event will be recorded in DR TB pharmacovigilance sheet
   • Immediately events those are serious in nature related to BdQ will be reported to PMDT focal person clinical/ HoD of pulmonology
   • In case of cardiac event, the focal person/nominated doctor from cardiology unit will be informed immediately by MDR Tb physician and any happening will be managed.
   • In case of any life threatening event, immediate clinical care will be instituted
   • A meeting will be held at PMDT site (involving relevant specialties) to discuss thoroughly this case and happening of event and further preventive measures will be discussed

- This event will be reported to provincial committee and simultaneously to federal level as it happens
- The provincial and federal team will remain in touch with PMDT team and will make sure that flow of reporting is being followed
- The federal team will further report these events to GDF/WHO or as required
- All side effects minor to major will be recorded at PMDT site and data will be analyzed quarterly to discuss findings for strengthening of pharmacovigilance framework
- The hard copies of pharmacovigilance recording sheet(scanned) will be shared with PTP/NTP on monthly basis with recording of all minor to major side effect

5.6:   Data Recording & Reporting

Recording and reporting will be done according to the norms for recording and reporting for PMDT. Standard NTP reporting and recording forms and mechanism will be used for patients on bedaquiline. Patients will be reported on main ENRS sheet and in the column of source of Drug i.e GLC/non GLC another option of BdQ will be added to report the progress of these patients on monthly basis. These patients will be reviewed and analyzed separately by placing a filter on BdQ source of Drug. WHO 2013 definitions in this cohort will be used as are being used currently. MDR TB unit will also share the separate ENRS to report BdQ patients separately along with pharmacovigilance sheet.

5.7:   Data Analysis

Interim analyses of culture conversion, unfavorable outcomes and adverse events will be done on the first cohort of 20 patients with completion of the intensive phase, this data will be reviewed by the WHO monitoring committee.

The following statistical analyses will be done:

1. Rates of sputum conversion and survival analysis for time to culture conversion.
2. Analysis of treatment outcomes.
3. Rates and severity of side effects.
4. Rates of relapse.
5. Univariate analysis to assess risk factors for unfavorable response and confounding factors will be investigated.

CHAPTER # 6: A New Anti TB drug Delamanid

Nitro-dihydro-imidazo-oxazole derivative

• Mechanism of action
– Inhibits M*tb* cell wall synthesis
– Highly active against intracellular M*tb* in macrophages
• No cross-resistance with any anti-TB drugs
• Pharmacology
– Half life 38 hours
– Metabolized by cytochrome enzymes (CYPA4)
– Metabolites regulated by plasma albumin
• Can prolong the QT interval (mean increase 14.4 ms, max. at 8 weeks)
Conditionally approved by EMA in November 2013

Dosage & Presentation

Dosage
Dosage • 100 mg twice daily (200 mg total daily dose) 7 days per week for 24 weeks • Can be taken at the same time as the other anti-TB drugs • Should be taken with a light meal

WHO Interim Guidance

MDR-TB patients in whom Delamanid may have a particular role include :
– Patients with additional resistance or intolerance to quinolones or injectable drugs and patients with XDR-TB
– Patients with extensive lesions and advanced disease
– Other patients deemed at higher risk for poor outcomes
The use of the drug in patients with extra-pulmonary MDR-TB may be considered, extrapolating from the data in patients with pulmonary TB.
Conditional recommendation, very low confidence in estimates of the effects (as for Bedaquiline)

Patients for whom the construction of a regimen with 4 likely effective SLD including a FQ and an injectable is not possible

      a. XDR-TB (resistance to FQ and at least one injectable)

      b. Pre-XDR-TB (resistance to FQ or injectables)

      c. Patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised

      d. Contact with a patient with a strain with resistance pattern of a, b, or c.

      e. Patients unable to tolerate MDR-TB drugs necessary for construction of the regimen

      f. Patients who are a "failure" of an MDR-TB regimen by WHO 2013 definitions

Other patients with high risk of unfavorable outcome

a. Other patients with high risk of unfavorable outcome

Patients with extensive or advanced disease (multiple cavities, bilateral lesions, or extensive parenchymal damage or multiple system involvement)

b. Patients with increased likelihood of treatment failure, or death (patients with low body mass index, HIV, diabetes, etc.)

c. Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (e.g. sites with extensive second-line drug resistance background)

Contra-indications

Absolute

• Known hypersensitivity to the drug

• Baseline ECG demonstrating a QTcF > 500 ms (repeated); or history of syncopal episodes, ventricular arrhythmias or severe coronary artery disease

• Serum albumin < 2.8 g/dL

• Refuse to consent

Relative

• Children <18 years

• Pregnancy and lactation

Caution

• When used with other QT prolonging drugs (Mfx, Cfz, LPV/r, ondansetron)

• When used strong inducers or inhibitors of the CYPA4

• No data on concommitant use with Bdq

Factors to be taken in consideration

Currently more experience with use of Bdq in XDR-TB than Dlm

• Long half-life of Bdq (5 months) :

    – Dlm cannot be used after Bdq before a wash out period of 6 months

    – Risk of potential monotherapy to Bdq when the treatment is stopped

• Increased risk of death in the Bdq arm of the clinical trial*

• Better safety profile of Dlm

• Dlm presents less drug-drug interaction with ART

• There is a potential cross-resistance between Cfz and Bdq

• Bdq and Dlm cannot be used in combination

Monitoring of patient under Delamanid

Baseline

• ECG (QTcF)

• Albuminemia

• Electrolytes (K+, Ca++, Mg+)

Follow-up

• ECG at least 2, 4, 8, 12 and 24

• ECG monthly if taking other QT prolonging drugs or strong CYPA4 inhibitors

• Electrolytes (K+; Ca++, Mg+) monthly

Monitoring for other drugs in the regimen Bacteriological monitoring Detection and management of adverse events Pharmacovigilance
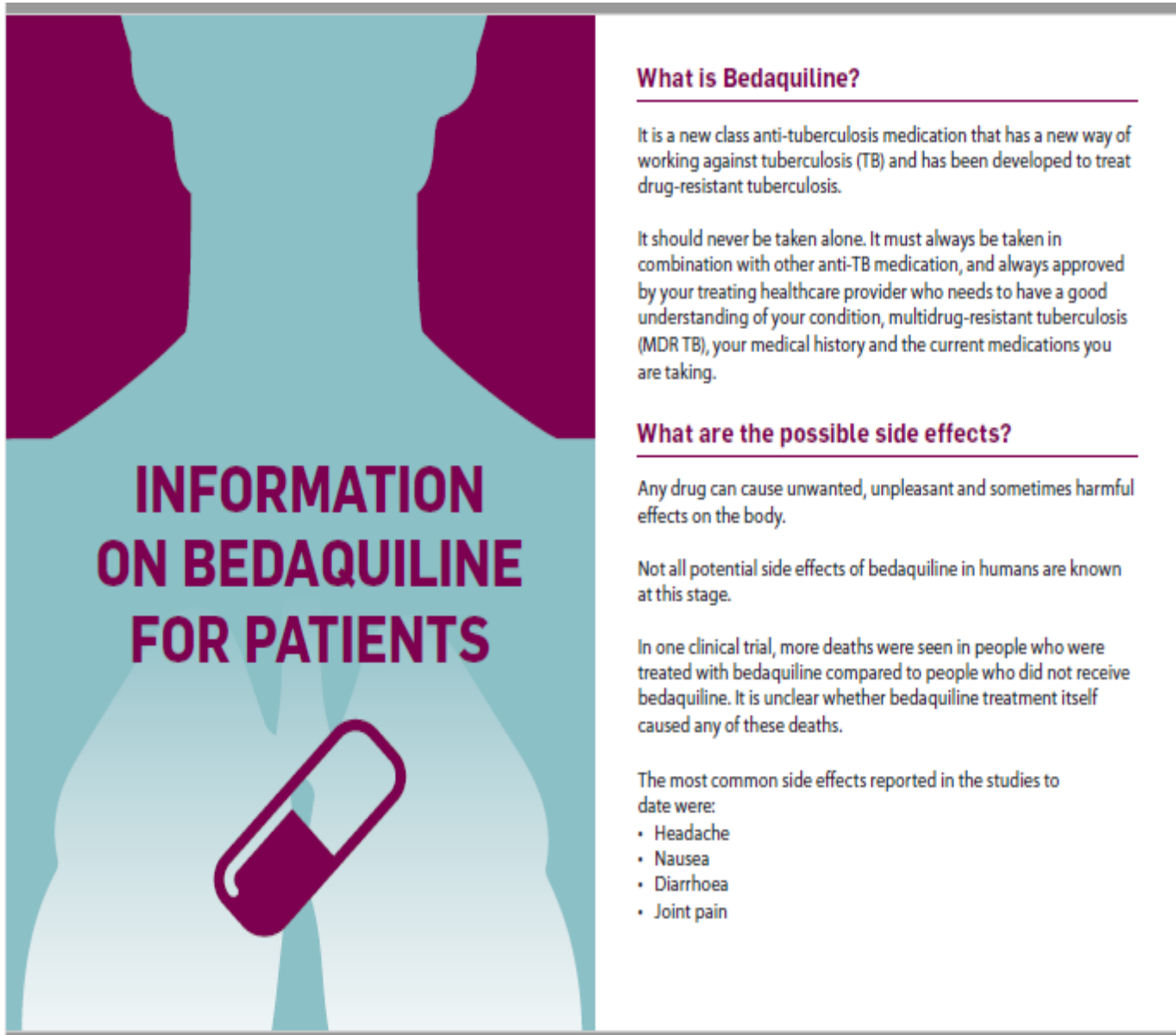
Conclusion & Recommendations

Available data show a good safety profile and potentially large indications

• Should be used with

    – Proper patient inclusion criteria

    – Adherence to the key principles of designing a MDR-TB regimen

    – Adequate monitoring and management of adverse drug reactions

    – Good pharmacovigilance

Additional chance of improved outcomes for MDR-TB

ANNEXURES:

Annex 1: Patient Information Sheet(courtesy of Swift Project)

INFORMATION ON BEDAQUILINE FOR PATIENTS

What is Bedaquiline?

It is a new class anti-tuberculosis medication that has a new way of working against tuberculosis (TB) and has been developed to treat drug-resistant tuberculosis.

It should never be taken alone. It must always be taken in combination with other anti-TB medication, and always approved by your treating healthcare provider who needs to have a good understanding of your condition, multidrug-resistant tuberculosis (MDR TB), your medical history and the current medications you are taking.

What are the possible side effects?

Any drug can cause unwanted, unpleasant and sometimes harmful effects on the body.

Not all potential side effects of bedaquiline in humans are known at this stage.

In one clinical trial, more deaths were seen in people who were treated with bedaquiline compared to people who did not receive bedaquiline. It is unclear whether bedaquiline treatment itself caused any of these deaths.

The most common side effects reported in the studies to date were:
- Headache
- Nausea
- Diarrhoea
- Joint pain

POSSIBLE SIDE EFFECTS

COMMON SIDE EFFECTS

- Headache
- Nausea
- Diarrhoea
- Joint pain

POTENTIALLY SERIOUS SIDE EFFECTS

Increase in "QT" interval: QT interval is an electrical measurement of how the heart functions and can be seen on an ECG (electrocardiogram). An abnormally prolonged QT interval increases the risk of heart rhythm disturbances, which in rare cases may cause cardiac arrest and sudden death. No significant clinical side effects due to heart rhythm disturbances could be detected in the current studies, but it is important to remember that there have not been enough studies yet to say whether this drug is completely safe or not. Each patient should have regular ECGs to monitor the electrical activity of their heart and to measure the QT interval.

Long QT interval can be caused by inherited conditions (called "Congenital Long QT syndrome"), or medications. Some common medications can cause this (including TB medications, or medications given against clinical depression, allergy, fungal or microbial infections). It is important to tell your healthcare provider about all the medications that you are using.

If you have:
1. a family history of heart disease, or
2. if you have heart disease yourself or
3. if you are on medication that could have effects on your heart, you should first discuss this with your healthcare provider.

Symptoms like fainting, feeling an irregular, fast or slow heartbeat, or seizures should be reported to your healthcare provider immediately.

Bedaquiline can cause inflammation (irritation) to liver and pancreas tissue. Some symptoms to look out for are abdominal or back pain, persistent nausea and indigestion. A later symptom could be oily, smelly stools. Much of this inflammation can occur without symptoms, so blood tests should be done regularly to monitor for the possible development of injury to the liver or pancreas.

Bedaquiline takes a long time to be removed by the body (It takes up to 5 months for half of the amount of the drug to be removed). Detectable levels of the drug could remain in your body for up to 2 years. The significance of this slow removal process is currently not known.

What to do in case of any possible side effect

You should tell your healthcare provider immediately about any side effect that you experience while taking bedaquiline. By acting quickly, the chances that the side effects continue or become worse can be reduced. Sometimes other medications can be given to reduce the side effects and/or make you feel more comfortable.

You will be treated with other medicines for your TB infection as recommended by your doctor/health care facility/government's TB programme. These other medications could also have side effects not listed here. When different TB medicines are used together they can sometimes have unexpected side effects.

Tell your healthcare provider right away if you have any problems

You have the right to ask any questions concerning the potential and/or known dangers of bedaquiline at any time. If additional information becomes available about the risks of taking bedaquiline you should be informed by your healthcare provider.

Bedaquiline and HIV treatment

If you are HIV positive, your healthcare provider will discuss with you whether it is better to delay starting HIV treatment or to treat you with a drug regimen for HIV that available data suggests is appropriate for use with bedaquiline. Only a few HIV positive subjects with MDR TB were enrolled in the clinical studies, but so far bedaquiline appeared to be generally safe and well tolerated in people living with HIV.

Annex 2: Informed Consent Form and Certificate of Consent

National TB Control Program, Government of Pakistan, Islamabad

(Use of Bedaquiline (A new Anti TB Drug) for Treatment of MDR-TB in Pakistan)

Treatment **Hospital:**

_____

 Department:

_____

Informed Consent Form for Patient

Read the below information before you decide to start taking bedaquiline and each time before your monthly visit. This information has been specially developed for you to explain about this new drug, its benefits and potential harms.

This information will be helpful in deciding to get treated with Bedaquiline for yourself and also for your physician. Below is the step wise information for your better understanding and one of your close friend/health worker or relative can read it for you if you are not able to read/understand.

What is the most important information you should know about bedaquiline?

MDR-TB is a serious disease that can result in death and for which there are few treatment choices. Bedaquiline is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) in people who have less treatment options available. More people treated with bedaquiline cleared TB from their sputum compared to people who did not receive bedaquiline. Around the globe this drug has been used and results reported are satisfactory.

It is important to complete the full course of treatment that will be given to you and not to skip any dose. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by bedaquiline or other medicines.

Serious side-effects related to Bedaquiline:

It is not known if bedaquiline is safe in:

- Children under 18 years of age
- Pregnancy
- In patients with heart, kidney, liver or other health problems.

Bedaquiline can cause some disturbance with rhythm of the heart, but your physician will take good care of it to reduce the risk of happening. Moreover, Bedaquiline can also cause liver problems, but your physician will keep regular checks for it.

Inform your Doctor if you have following problems, before taking Bedaquiline:

- You have had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem.
- You have liver or kidney problems or any other medical conditions, including HIV infection.

- You (in case of female of child bearing age) are pregnant or plan to become pregnant.
- You are breastfeeding or plan to breastfeed. You and your doctor should decide if you will take bedaquiline or breastfeed.
- You are taking any prescription and non-prescription medicines, vitamins and herbal supplements.

How should you take bedaquiline?

- Bedaquiline must always be taken with other medicines to treat TB. Your doctor will decide which other medicines you should take with bedaquiline.
- Always take bedaquiline with a light meal.
- Swallow the tablets whole with water.
- You will take Bedaquiline for 24 weeks(6 months) and rest of the treatment will continue for 20 months at least(with 8 months injectable) as advised by your doctor
- You will need to take four tablets of bedaquiline daily for two weeks, and two tablets on Mondays, Wednesdays and Fridays for a further five and a half months thereafter.
- If required your Doctor will advise you for admission in hospital, otherwise your treatment will be provided under directly observed treatment (DOT). You will get a good care by team with patient centered approach and minor to major side effects will be monitored closely.
- It is very important and crucial for you to complete the treatment and take medicines as advised by your doctor. If you do not complete the total 24 weeks of bedaquiline your treatment may not work as well and your TB may be harder to treat.
- Never miss a dose of Bedaquilline, if for some reason you miss a dose during the first two weeks of treatment, do not make up the missed dose and continue the usual dosing schedule. From three weeks onward, if a 200 mg dose is missed, you should take the missed dose as soon as possible and then continue the three times a week regimen. If any confusion or not clear, inform the person responsible for your treatment right away, they will tell further guide you.

What should you avoid while taking bedaquiline?

- There are some medications that cannot be taken safely with bedaquiline.

Make sure to inform your doctor if you are taking any medicines or if other medicines are recommended to you by any health care practitioner while you are on treatment for

TB with bedaquiline.

Alcohol or other substance/ Nasha should not be taken while on treatment

What are the possible side-effects of bedaquiline?

- Common side-effects of bedaquiline include nausea, joint pain, headache, abnormal laboratory test associated with damage to the pancreas, coughing up blood, chest pain, loss of appetite, and/or rash.
- Changes in heart rhythm, in this case tell your health care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.
- Liver problems (hepatotoxicity). Liver toxicity can present in many ways. Tell your doctor of symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual

tiredness, loss of appetite, light colored stools, dark colored urine, yellowing of your skin or yellowing of the white of your eyes.

- It is possible that it may also cause some problems that we are not aware of.
- However, you will be followed closely for any unwanted effects or any problems.
- Other medicines to decrease the symptoms of the side-effects or reactions may also be given.
- Always tell your health care provider/doctor as early as possible of any side-effects or problems you are having.
- You will get monitoring tests as for other MDR TB patients, but additionally heart monitoring and liver tests will be done.
- Sometimes because of side-effects bedaquiline or other drugs may need to be stopped.

General information about the risk versus the benefit of taking bedaquiline

BENEFIT: There is a greater chance that you will be cured of tuberculosis if you have taken medicine regularly. You will possibly also become better very much sooner than if you only took the standard medicines for treatment of resistant TB.
Also, it is probably less likely that the drugs you are taking will develop resistance if you are taking bedaquiline

RISK: It is possible that you will be at greater risk of not feeling well than you would otherwise because of certain side-effects due to the drug. It is possible that adverse side-effects could be serious and even result in death. But results from other countries with Bedaquilline treatment are satisfactory.

Confidentiality and sharing of information

- Because bedaquiline is a new drug for which we have limited experience, we are collecting information on patients taking it.
- The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.
- Any information collected to help us better use the drug in future patients will be unlinked to your name (made anonymous) before we share or analyze it.

Costs

Bedaquiline and other drugs in treatment of MDR TB will be provided free of charge to you. Moreover, you will receive social support during the course of treatment.

Right to refuse or withdraw from Treatment

You have the right to agree or disagree with treatment of Bedaquiline and this will not affect your treatment at this clinic in any way. You may also choose to discontinue it at any point for any reason. You will still have all the benefits that you would otherwise have at this clinic.

Contact person details:

If you have any questions at any point during or before the treatment, you may contact any of the following persons:

Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name of responsible physician: _____

Name of clinic/hospital/institution: _____

If the participant is illiterate but gives oral consent, a witness must sign the relevant section below. The person going over the informed consent must sign this form.

Certificate of Consent

I have read the provided information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive bedaquiline for treating the drug-resistant tuberculosis disease that I am suffering from.

Print   Name   of   Patient:

_____

Signature   and   or   Thumb   impression   of   Patient:

_____

Date: _____
                          Day/month/year

If illiterate, a literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

I have witnessed the accurate reading of the consent form to the potential recipient of bedaquiline, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____ AND Thumbprint of patient

Signature of witness: _____

Date: _____
                          Day/month/year

NOTE: (This page is part of the full information for consent taking process)

Annex 3: Check list for MDR TB Physician

S. #	Parameters	Tick Yes or No
1	Patient is at least 18 years old and under 65 years of age	
2	Patient is known or suspected to be diseased with a multiple resistant strain of tuberculosis and therefore eligible for treatment with second-line anti-TB drugs.	
3	Additional laboratory data has been obtained on the susceptibility profile of the patient's TB isolate to the following agents: fluoroquinolones (ofloxacin and moxifloxacin), and second-line parenteral agents (kanamycin, amikacin and capreomycin).	
4	The drug resistance profile of the patient's isolate suggests that the WHO standard recommended regimen for treatment of MDR-TB cannot be provided.	
5	Clinically significant ventricular arrhythmia is absent.	
6	Baseline and repeat ECG shows normal QT interval.	
7	Aminotransferase(AST) and total bilirubin within normal limits	
8	The patient's serum albumin, potassium, calcium, and magnesium have been obtained at baseline and levels are within normal limits.	
9	Informed consent for treatment with bedaquiline has been obtained	

Note:

- If the answer is 'yes' to all questions, the patient can be enrolled on treatment with bedaquiline as per protocols.
- If the answer is 'no' to any of the above, further consideration and review is needed before enrolment in a treatment regimen with bedaquiline.
- Getting a 'no' response to any of the above is not an absolute contraindication to using bedaquiline, only that the situation should be reviewed and the risk benefit of bedaquiline be reconsidered under the circumstance.

References:

1.Press release on bedaquiline. 31 December 2012. US Food and Drug Administration. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm, accessed 28 March 2014).

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