World Health Organization

BEDAQUILINE

Use of bedaquiline in children and adolescents with multidrug- and rifampicin-resistant tuberculosis - Information note

Objective

To provide practical guidance on the administration of bedaquiline in children and adolescents in the context of the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB), in line with the latest World Health Organization (WHO) recommendations, dosing guidance and available formulations.

Target audience

Doctors, clinicians, paediatricians, nurses, pharmacists, parents and caregivers of children with MDR/RR-TB, community health workers, programme managers, implementing partners and partners providing technical assistance.

WHO recommendations for bedaquiline in children and adolescents

The United States Food and Drug Administration granted accelerated approval for bedaquiline in 2012 for the treatment of adults aged 18 years and over with multidrug-resistant pulmonary TB (MDR-TB) for whom an effective treatment regimen could not otherwise be composed *(1)*. This approval was based on phase IIb trial data and made bedaquiline the first medicine from a new class approved with a TB indication in over 40 years.

Since then, additional evidence has been generated on the use of bedaquiline for the treatment of MDR/RR-TB in both adults and children. Bedaquiline has played an increasingly important role in TB treatment as a component of both shorter and longer regimens, and has allowed the move away from injectable-containing regimens to all-oral regimens *(2)*.

Bedaquiline – a key medicine in WHO-recommended regimens

- Bedaquiline is now recommended by WHO for the treatment of MDR/RR-TB in adults and children of all ages *(3)*.
- Bedaquiline is a component of the **9-month all-oral regimen**, which is the treatment of choice for eligible people aged under 14 years with MDR/RR-TB rather than longer (18 month) regimens.
- For people aged 14 years and over with MDR/RR-TB, WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) rather than the 9-month or longer (18 month) regimens. In cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued *(4)*.
- Bedaquiline is a **group A medicine** and a core component of **longer individualized regimens** for people who are not eligible for the 9-month all-oral or BPaLM/BPaL regimens.

> Bedaquiline can be used as part of short and long all-oral WHO-recommended regimens for people with MDR/RR-TB of all ages.

Duration

- Bedaquiline is usually given for 6 months. This may be extended to the entire duration of the 9-month all-oral regimen if the initial phase of the regimen is extended from 4 to 6 months, if sputum is positive after 4 months of treatment.
- When used as part of a longer regimen in people with fluoroquinolone resistance or with limited treatment options, the extension of bedaquiline beyond 6–9 months may be considered (off-label use), with strict baseline and follow-up monitoring. For children, this should be done in consultation with an expert in paediatric drug-resistant TB.

9-month all-oral regimen: Initial phase: 4–6 months of bedaquiline, levofloxacin or moxifloxacin, clofazimine, pyrazinamide, ethambutol, high-dose isoniazid, and ethionamide (4 months) or linezolid (2 months).

Continuation phase: 5 months of levofloxacin or moxifloxacin, clofazimine, pyrazinamide and ethambutol.

Group A medicines: Include levofloxacin or moxifloxacin, **bedaquiline** and linezolid. These medicines were found to be highly effective in improving treatment outcomes and reducing deaths. It is strongly recommended that they are used for all people with MDR/RR-TB eligible for longer regimens unless there is a toxicity issue or drug resistance.

Longer individualized regimens: As a group A medicine, bedaquiline should be included in individualized MDR/RR-TB regimens for both fluoroquinolone-susceptible and fluoroquinolone-resistant treatment, unless bedaquiline resistance has been detected.

Possible individualized MDR/RR-TB regimens for children of all ages and adolescents can be found in Section 5.3.2.4 (Table 5.12) of the WHO Operational Handbook on Tuberculosis. Module 5: Management of Tuberculosis in Children and Adolescents *(5)*.

Special situations

Children and adolescents living with TB and HIV

Antiretroviral therapy regimens including integrase inhibitors such as dolutegravir are the best option for adults and children living with HIV and receiving bedaquiline, as clinically significant drug–drug interactions are not expected. Antiretroviral therapy regimens including efavirenz (EFV) should be avoided in adults and children on bedaquiline, because EFV substantially lowers the concentrations of bedaquiline *(6)*.

Co-treatment with lopinavir/ritonavir may result in elevated bedaquiline exposure, but experience has shown that this does not result in an increase in adverse effects so it may be considered with careful monitoring *(7, 8)*.

Children with malnutrition

Bedaquiline can be used safely in malnourished children. All WHO recommendations related to nutritional care and support apply.

Concomitant use of bedaquiline and delamanid

Bedaquiline and delamanid can be used together in people with MDR/RR-TB, including children, with careful electrocardiogram (ECG) monitoring.

Data in adults have shown that the combination of bedaquiline and delamanid does not result in a marked increase in adverse events, including QT prolongation (on the ECG). In people with limited therapeutic options, data on concurrent use have shown increased survival rates *(9, 10)*. Concomitant use of bedaquiline and delamanid in children is expected to be as safe as in adults.

Penetration of the blood–cerebrospinal fluid barrier

Some studies suggest that bedaquiline and its M2 metabolite penetrate the cerebrospinal fluid of people with pulmonary TB *(11)*, but the role for bedaquiline in the treatment of TB meningitis remains unclear and requires additional studies.

Dosing

Updated dosing guidance for the use of bedaquiline in children of all ages is included in the WHO Operational Handbook on Tuberculosis. Module 5: Management of Tuberculosis in Children and Adolescents (Annex 6) *(5)* and Module 4: Treatment – Drug-resistant Tuberculosis Treatment (Annex) (see Table 1) *(12)*.

Bedaquiline is usually administered daily for the first 2 weeks, and then 3 times a week.

An alternative dosing strategy for bedaquiline as part of the BPaLM/BPaL regimen for people aged 14 years and over is proposed based on the dosing scheme used in the ZeNix trial. As part of the BPaLM/BPaL regimen, 200 mg bedaquiline may be administered daily for 8 weeks, followed by 100 mg daily. This alternative dosing strategy may be more convenient for both patients and health-care providers because it allows daily dosing of all medicines in the regimen. No data are available on a daily dosing strategy for bedaquiline in people aged under 14 years with MDR/RR-TB.

WHO guidance on bedaquiline dosing may be updated as further evidence emerges, especially for younger people, for whom studies are ongoing.

For bedaquiline dosing in preterm and low-birth-weight infants weighing less than 3 kg, and ideally for infants weighing 3 to <5 kg, advice from an expert in paediatric drug-resistant TB should be sought.

A joint age- and weight-based approach to bedaquiline dosing is indicated for children weighing 3 to <16 kg. This is important because bedaquiline is metabolized by enzymes, and enzyme function may be immature in young children, resulting in lower medicine clearance. Doses are adjusted based on age (under 3 months, 3 to <6 months, ≥6 months) to avoid too high bedaquiline concentrations and a consequent risk of adverse events.

Bedaquiline is administered with food, ideally a high-fat meal, as this has been shown to lead to a two-fold increase in bioavailability (how much is absorbed) *(13)*. Taking bedaquiline with any food is sufficient, however, and the lack of a high-fat meal should not be a barrier to taking bedaquiline.

Normally, bedaquiline is taken daily for the first 2 weeks, and then 3 times a week at a halved dose. If MDR/RR-TB treatment is interrupted after the first 2 weeks of treatment, studies suggest that no new loading dose (corresponding to the initial higher dose given in the first 2 weeks) is needed for interruptions with a duration of less than 2 weeks. For interruptions with a duration between 2 weeks and 1 month, between 1 month and 1 year, and more than 1 year, reloading periods of 3 days, 1 week and 2 weeks, respectively, may be used. Bedaquiline has a long terminal half-life, and restarting after an interruption without a loading dose could increase the risk of suboptimal treatment outcomes and development of resistance *(14)*. Additional information on the management of bedaquiline dose interruptions can be found in the WHO Operational Handbook on Tuberculosis. Module 4: Treatment – Drug-resistant Tuberculosis Treatment (Chapter 5.2.4) *(12)*.

> The use of the child-friendly formulation of bedaquiline (20 mg dispersible tablet) is preferred in young children, but its non-availability should not be a barrier to treating children with MDR/RR-TB. Administering 100 mg tablets crushed and suspended in water does not have any impact on the amount of medicine absorbed by the body.

For children in most weight bands, dosing is provided using either the child-friendly formulation (20 mg dispersible tablet) or the adult 100 mg tablet formulation (Table 1). When available, bedaquiline 20 mg dispersible tablets should be prioritized for the treatment of young children with MDR/RR-TB over the adult 100 mg formulation, which must be manipulated (split, crushed or dissolved) before administration. Non-availability of the child-friendly formulation should not be a barrier to treating children with bedaquiline. Bedaquiline 100 mg tablets crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole, meaning the body absorbs the same amount of bedaquiline, regardless of how the tablets are administered *(15)*. Indirect bioequivalence studies have shown that the 20 mg and 100 mg tablets have the same bioavailability *(16)*; therefore, they can be used interchangeably at the same total milligram dose. The use of the 100 mg formulation may reduce the pill burden in some children.

Table 1. WHO guidance on bedaquiline dosing in people with MDR/RR-TB

Weight bands	Age (months)	Formulation and dose[a]		
		20 mg tab	100 mg tab	
			Dose *(100 mg in 10 mL = 10 mg/mL)*	Alternative dosing option for BPaLM/BPaL (≥ 14 years)
3–<7 kg	0 to <3 months	1.5 od for 2 weeks; then 0.5 od M/W/F	3 mL od for 2 weeks; then 1 mL od M/W/F[b]	-
	≥ 3 months	3 od for 2 weeks; then 1 od M/W/F	6 mL od for 2 weeks; then 2 mL od M/W/F[b]	-
7–<10 kg	0 to <3 months	1.5 od for 2 weeks; then 0.5 od M/W/F	3 mL od for 2 weeks; then 1 mL od M/W/F[b]	-
	3 to <6 months	3 od for 2 weeks; then 1 od M/W/F	6 mL od for 2 weeks; then 2 mL od M/W/F[b]	-
	≥6 months	4 od for 2 weeks; then 2 od M/W/F	8 mL od for 2 weeks; then 4 mL od M/W/F[b]	-
10–<16 kg	3 to <6 months	3 od for 2 weeks; then 1 od M/W/F	6 mL od for 2 weeks; then 2 mL od M/W/F[b]	-
	≥6 months	6 od for 2 weeks; then 3 od M/W/F	12 mL od for 2 weeks; then 6 mL od M/W/F[b]	
16–<30 kg	-	10 od for 2 weeks; then 5 od M/W/F	2 od for 2 weeks; then 1 od M/W/F	-
30–<46 kg	-	20 od for 2 weeks; then 10 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	-
≥ 46 kg	-	-	4 od for 2 weeks; then 2 od M/W/F	200 mg daily (od) for 8 weeks; then 100 mg dose daily (od)

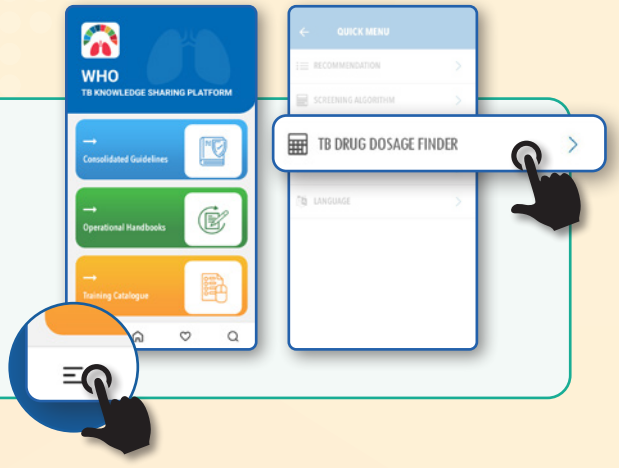
BPaLM/BPaL: regimen composed of bedaquiline (B), pretomanid (Pa), linezolid (L), with or without moxifloxacin (M); kg: kilogram; mL: milliliter; mg: milligram; M/W/F: Monday, Wednesday, Friday; od: once daily; tab: tablet.

[a] Bedaquiline is given at a loading dose for the first 2 weeks, followed by a maintenance dose in the continuation phase, which is normally 22 weeks.

[b] The number of mL in the table reflects the dose to provide after dissolving crushed adult tablets in 10 mL of water.

A drug dosage finder to facilitate dosing of second-line medicines, including bedaquiline is available here if the WHO TB Knowledge Sharing Platform app is installed on your mobile phone.

To download the app on your mobile phone, click here for **iOS** and here for **Android**.



Bedaquiline 20 mg dispersible tablets

Tablets are functionally scored. They can be split at the scored line into two equal halves of 10 mg each.

Tablets, whether taken whole or dispersed, are palatable, which increases acceptability for children *(2)*.

Tablets are administered orally as whole or dispersed tablets, or after crushing and mixing with food (see below).

If tablets are administered with other medicines after dispersing them in water, ensure all tablets are properly dispersed, as different tablets may have different dissolving rates. Consider whether the palatability of the resulting mixture may affect administration of the medicines: if one of the medicines is bitter, the resulting mixture will also taste bitter, impacting on acceptability.

Tablets can be administered through a nasogastric tube (gauge ≥8 French) immediately after dispersing in uncarbonated water.[1]

Dispersed in water

- Disperse tablets in water (up to 3 mL water per tablet, maximum 5 tablets in 5 mL water) in a drinking cup.
- Mix contents well until tablets are completely dispersed, and then orally administer the contents immediately with food.
- To aid with administration, mix the dispersed solution with at least 5 mL of beverage (e.g. milk product, fruit juice, carbonated beverage) or 1 teaspoon of soft food (e.g. yogurt, apple sauce, mashed banana, porridge), and then orally administer the contents of the cup immediately.
- To ensure no tablet residue is left in the cup, rinse with 5 mL beverage or add more soft food, and orally administer the contents immediately.

Crushed and mixed with soft food

- Crush tablets.
- Add to soft food (e.g. yoghurt, apple sauce, mashed banana, porridge, peanut butter, peanut nutritional supplementation), mix and administer immediately.
- Add more soft food to ensure no residue is left in the container, mix and then administer immediately.

Bedaquiline 100 mg tablets

Tablets are not scored.

Tablets are intended to be swallowed whole. If the person cannot swallow whole tablets, and the 20 mg dispersible tablet formulation is not available, the 100 mg tablet can be administered after being crushed and suspended in water (10 mL per tablet), followed by vigorous stirring and shaking before administration.

It is possible to prepare sugar-containing and sugar-free **extemporaneous liquid formulations** of bedaquiline that permit dose titration for children and for people who cannot swallow whole tablets *(17)*. These use easily accessible ingredients and equipment and can be prepared in any pharmacy or dispensary. Sugar-containing and sugar-free extemporaneous suspensions can be stored in amber prescription bottles for 15 days at room temperature and 30 days up to 30 °C, respectively. Preparation instructions for these formulations are given in Annexes 1 and 2.

Extemporaneous preparation or compounding refers to the preparation of a medicine product in a pharmacy according to a specific recipe in which calculated amounts of ingredients, including the medicine, are made into a homogeneous mixture.

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204384s013lbl.pdf for more information.

For parents and caregivers administering bedaquiline to children at home:

- If the dose corresponds to a whole 100 mg tablet and the child cannot swallow tablets, the bottom of a clean bottle or cup can be used to crush the tablet, which can then be mixed with soft food or dispersed in water.
- If water is used to facilitate administration, ensure it is boiled, filtered or bottled. If another liquid (e.g. fruit juice) is used, ensure it is bottled or prepared with boiled, filtered or bottled water.
- Tools used to prepare the suspension should be cleaned before and after use, preferably with hot water and soap, or with an alcohol- or bleach-based cleaning solution.
- Ensure bedaquiline tablets are stored in the containers provided by the clinic in a cool, dry place, out of reach of children.

Clinical monitoring and management of adverse events

Routine clinical and safety monitoring for MDR/RR-TB treatment in children should generally follow the recommended approach in adults and should be guided by the known adverse event profiles of the medicines included in the regimen. The most common adverse events of bedaquiline are headache, nausea, QT interval prolongation and arthralgia. Elevated transaminases are also reported, but less commonly.

People receiving bedaquiline in combination with other potentially QT-prolonging medicines (e.g. clofazimine, delamanid or a fluoroquinolone, especially moxifloxacin) should have regular ECG monitoring, ideally at baseline and then monthly while on treatment and additionally as clinically indicated. Given the composition of currently recommended regimens, most people being treated for MDR/RR-TB will be receiving one or more QT-prolonging medicines and need ECG monitoring.

Management of **QTcF** prolongation in children should follow the same steps as in adults, with symptom assessment, repeat ECG, electrolyte assessment and electrolyte replacement if relevant, nutritional assessment, thyroid function testing (if on ethionamide or *P*-aminosalicylic acid), and review of other medicines and possible clinical conditions. The use of paediatric chest leads in young children with small chests may improve accuracy; alternatively, leads can be cut to fit the chest.

A QTcF over 450 ms is considered prolonged. A QTcF over 500 ms raises the risk of a potentially life-threatening arrhythmia, and serious consideration should be given to withholding potentially QT-prolonging medicines until the QT interval has improved, or withdrawal of the culprit medicine as needed. The risk of a severely elevated QT interval (QTcF ≥500 ms) does not appear to be high in children or adolescents *(12)*.

Ideally, children treated with bedaquiline and other potentially hepatotoxic medicines should have alanine aminotransferase (ALT) with or without aspartate aminotransferase (AST) and bilirubin levels measured at baseline. A possible approach to monitoring for hepatotoxicity is to repeat at least ALT every 4 weeks (or monthly) for the first 6 months, every 8 weeks thereafter, and additionally as clinically indicated. Although the risk of serious asymptomatic hepatoxicity in children is not high, the lack of facilities for (frequent) monitoring of liver function tests should not be a barrier to prescribing bedaquiline.

Monthly monitoring of body weight is especially important in children and adolescents. The dose of bedaquiline and other medicines should be adjusted as the child gains weight. In infants, depending on their age, more regular monitoring of body weight is advised.

Adherence counselling and support is a crucial part of effective care for children and adolescents with MDR/RR-TB and their families *(18)*. Information on adherence counselling and support and clinical monitoring for children and adolescents treated with bedaquiline and other second-line TB medicines can be found in the WHO Operational Handbook on Tuberculosis. Module 4: Treatment – Drug-resistant Tuberculosis Treatment *(12)* and Module 5: Management of Tuberculosis in Children and Adolescents *(5)*.

QTcF (Fridericia's formula) is a formula calculated based on the QT interval on the ECG and guides the management of children receiving any combination of potentially QT-prolonging medicines.

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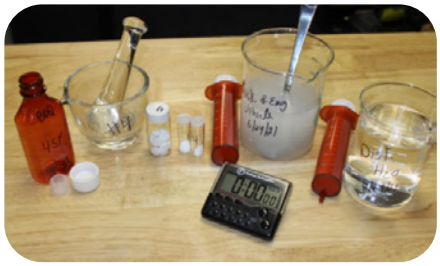
Annex 1. Preparation of sugar-free extemporaneous suspension of bedaquiline (20 mg/mL) using 100 mg tablet

Materials



Preparing a modified starch[2] sugar-free vehicle

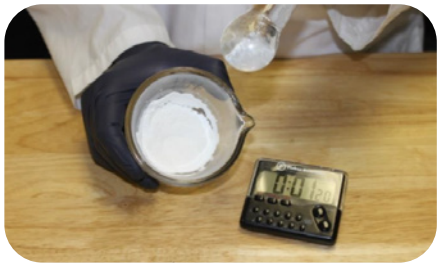
1. Measure 236 mL (8 oz) distilled water into a suitable container.

2. Add 11.5 g modified starch[2] powder.

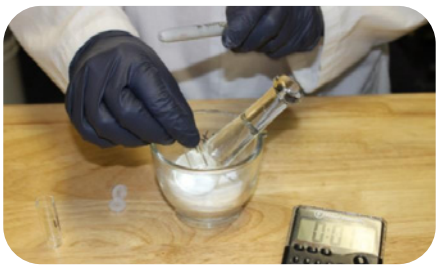
3. Mix well with a spoon for 30 s. Let the mixture sit for at least 5 minutes before use. Mix again just before use.

Preparing bedaquiline sugar-free formulation

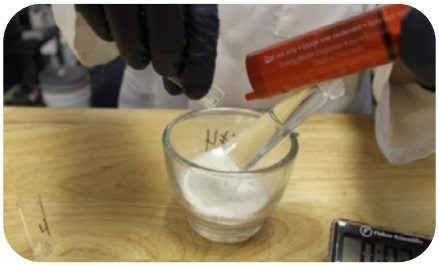
4. Grind 20 tablets (100 mg each) to a fine powder with a mortar and pestle.



5. Add 100 mg methyl paraben, 100 mg potassium sorbate, 125 mg citric acid and 125 mg sodium saccharin to the ground tablets in the mortar and mix all the powders well with the pestle.

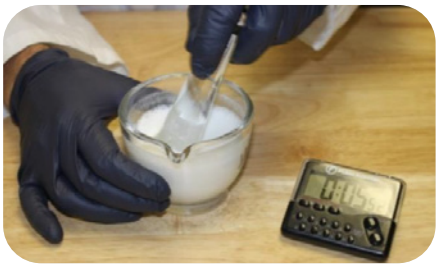


6. Add 20 mL distilled water to the mortar using an oral syringe. Mix the powder with a pestle to form a uniform suspension.



7. Add an additional 30 mL water using an oral syringe and mix to form a uniform suspension.

8. Using an oral syringe, transfer 44 mL modified starch[2] sugar-free vehicle to the mortar and mix to form a uniform suspension.



9. Transfer the final contents with a total volume of 100 mL from the mortar into an amber bottle. The sugar-free extemporaneous suspensions can be stored for 30 days in amber prescription bottles up to 30 °C.

[2] In the paper by Taneja et al. that describes the development of the extemporaneous formulation method, Thick & Easy ® was used as the modified starch sugar-free vehicle (Taneja R, Nahata MC, Scarim J, et al. Stable, compounded bedaquiline suspensions to support practical implementation of pediatric dosing in the field. Int J Tuberc Lung Dis. 2023;27(3):189–194).

Annex 2. Preparation of sugar-containing extemporaneous suspension of bedaquiline (20 mg/mL) using a 100 mg tablet

Video instructions for this preparation are available at:

https://vimeo.com/788818062

Materials

Preparing simple syrup (65% w/w) from sugar (sucrose)

1. Weigh 255 g (300 mL if measured by volume) food-grade sugar (sucrose) into a container.

2. Add 135 mL hot distilled water and mix well until sugar is dissolved.

3. Cool syrup to ambient room temperature.

Alternatively, instead of following Steps 1–3, commercially available simple syrup can be used.

Preparing bedaquiline suspension in a sugar-containing syrup

4. Grind 20 tablets (100 mg each) to a fine powder with a mortar and pestle.

5. Mix the powder with a small amount (15 mL added using an oral syringe) of syrup prepared in Steps 1–3 above to form a uniform paste. Alternatively, commercially available simple syrup can be used.

6. Add sugar syrup in increasing amounts while mixing thoroughly until total combined amount of vehicle added is 96 mL.

7. Transfer final contents with total volume of 100 mL from the mortar into an amber bottle. The sugar-containing extemporaneous suspension can be stored for 15 days in amber prescription bottles at room temperature.

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