World Health Organization

DELAMANID

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

Objective

To provide practical guidance on the administration of delamanid 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 delamanid in children and adolescents

The European Medicines Agency granted conditional approval to delamanid in 2014 "as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis in adult patients (≥18 years of age) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability" *(1)*. This made delamanid the second new medicine from a new class approved with a TB indication, following on from bedaquiline.

Since then, additional evidence has been generated on the use of delamanid for the treatment of MDR/RR-TB in both adults and children. Its use has expanded the list of medicines available to design all-oral longer individualized regimens for people with MDR/RR-TB, moving away from toxic injectable agents. The availability of delamanid is particularly important for people, including children, with limited options due to a more extensive resistance profile.

> Delamanid can be used as part of individualized longer regimens for people of all ages with MDR/RR-TB.

Delamanid – a medicine for people of all ages with limited treatment options

- Delamanid is now recommended by WHO for the treatment of MDR/RR-TB in adults and children of all ages *(2, 3)*.
- Delamanid is a **group C medicine** and can be used as part of **longer individualized regimens** for people with MDR/RR-TB, including children and adolescents, who are not eligible for the 9-month all-oral regimen or the 6-month regimen composed of bedaquiline, pretomanid and linezolid, with or without moxifloxacin (BPaLM/BPaL).
- As a group C medicine, delamanid can be included in MDR/RR-TB regimens when a treatment regimen cannot be composed of **group A or B** agents alone, due to resistance or intolerance.

Duration

- Delamanid is usually given for 6 months. The duration may be extended beyond 6 months (off-label use) in people, including children, with fluoroquinolone resistance or with limited treatment options. Studies undertaken between 2020 and 2022 showed that the use of delamanid beyond 6 months (when given alongside other medicines, including bedaquiline) is safe *(4, 5)*.

Group A medicines: Include levofloxacin or moxifloxacin, bedaquiline and linezolid.

Group B medicines: Include clofazimine and cycloserine or terizidone.

Group C medicines: Include ethambutol, **delamanid,** pyrazinamide, imipenem-cilastatin or meropenem in combination with clavulanic acid, amikacin or streptomycin (only used as salvage therapy in children and adolescents aged under 18 years), ethionamide or prothionamide and *P*-aminosalicylic acid. Group C medicines are included in longer regimens if the regimen cannot be composed of Group A and B medicines alone.

Longer individualized regimens: Examples of 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 *(6)*.

Special situations

Children and adolescents living with TB and HIV

Delamanid can be administered safely to people with HIV, including children, on antiretroviral therapy who are also receiving MDR/RR-TB treatment *(7)*. When administered with strong CYP3A inhibitors (e.g. lopinavir/ritonavir), frequent electrocardiogram (ECG) monitoring should be considered.

Children with malnutrition

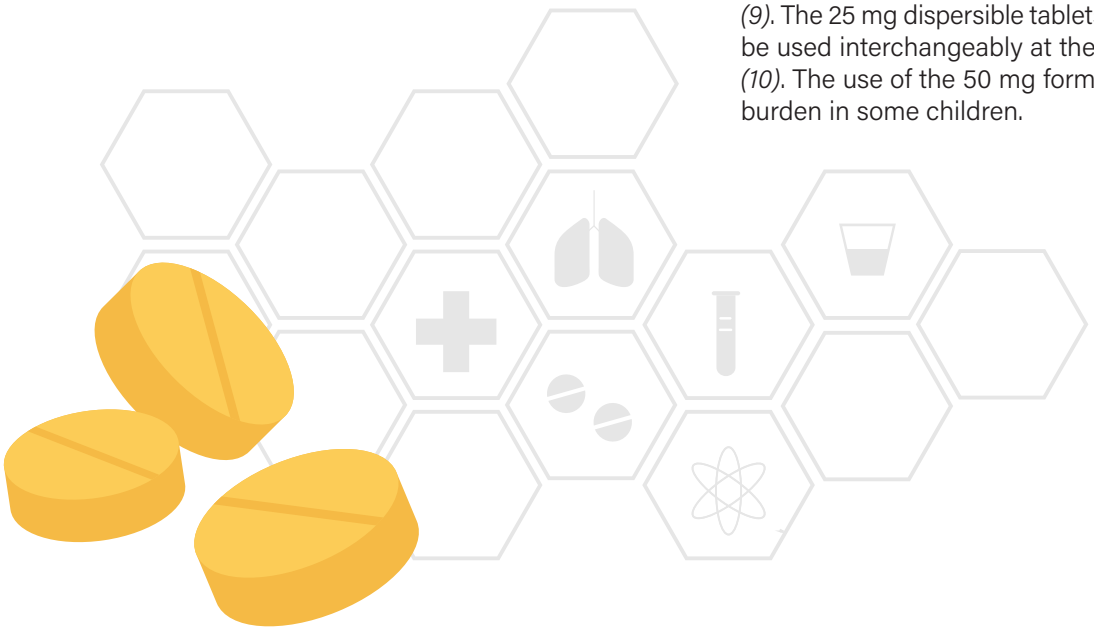
Delamanid can be used safely in malnourished children. All WHO recommendations related to nutritional care and support apply.

Concomitant use of bedaquiline and delamanid

Bedaquiline and delamanid can be used together in people with MDR/RR-TB, including children, with careful 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 *(4, 5)*. Concomitant use of bedaquiline and delamanid in children is expected to be as safe as in adults.

> The use of the child-friendly 25 mg delamanid dispersible tablet is preferred in young children, but its non-availability should not be a barrier to treating children with MDR/RR-TB. If necessary, 50 mg tablets can be dissolved in water and administered without any impact on the amount of medicine absorbed by the body.



Dosing

Updated dosing guidance for the use of delamanid 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) *(6)* and Module 4: Treatment – Drug-resistant Tuberculosis Treatment (Annex) *(8)* (see Table 1).

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

For delamanid 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 delamanid dosing is indicated for children weighing 5 to <10 kg. This is important because delamanid is metabolized by enzymes, and enzyme function may be immature in young children, especially those aged under 3 months, resulting in lower medicine clearance. Doses for children aged under 3 months are lower than doses for children aged 3 months and over to avoid too high delamanid concentrations and a consequent risk of adverse events.

For children weighing 16 to <30 kg, a 50 mg morning dose and a 25 mg evening dose 12 hours apart are recommended to achieve target exposures using the available formulations.

Delamanid should be administered with food, ideally a high-fat meal, as this has been shown to increase absorption of the medicine. Taking delamanid with any food is sufficient, however, and the lack of a high-fat meal should not be a barrier to taking delamanid.

For children in most weight bands, dosing is provided using either the child-friendly 25 mg dispersible tablet or the adult 50 mg tablet. When available, dispersible tablets should be prioritized for the treatment of young children with MDR/RR-TB over the adult 50 mg formulation. Non-availability of the child-friendly formulation should not be a barrier to treating children with delamanid. Delamanid 50 mg tablets dissolved in water have been shown to be equally absorbed by the body as tablets swallowed whole *(9)*. The 25 mg dispersible tablets and the 50 mg tablets can be used interchangeably at the same total milligram dose *(10)*. The use of the 50 mg formulation may reduce the pill burden in some children.

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

Weight bands	Age (months)	Formulation and dose	
		25 mg dt	50 mg tab[a] (50 mg in 10 mL = 5 mg/mL)
3–<5 kg	-	1 od	5 mL (0.5 tab) od
5–<10 kg	<3 months	1 od	5 mL (0.5 tab) od
	≥3 months	1 bd	5 mL (0.5 tab) bd
10–<16 kg	-	1 bd	5 mL (0.5 tab) bd
16–<30 kg	-	2 morning 1 evening	10 mL (1 tab) morning 5 mL (0.5 tab) evening
30–<46 kg	-	2 bd	1 bd
≥ 46 kg	-	-	2 bd

bd: two times a day; dt: dispersible tablet; kg: kilogram; mg: milligram; mL: milliliter; od: once daily; tab: tablet.

[a] The number of mL in the table reflects the dose to provide after dissolving adults 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**.

Delamanid 25 mg dispersible tablets

Tablets are not scored.

Tablets, whether taken whole or dispersed, are palatable, which increases acceptability for children.

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.

Administration

- Tablets are administered orally whole or dispersed in water.

To administer dispersed tablets

- Disperse using up to 10 mL water (approximately 1 tablespoon) per 25 mg dispersible tablet.
- Wait until the tablets dissolve completely (approximately 30 s) and swirl gently to make a uniform suspension.
- Administer the resulting whitish suspension immediately.
- Add a further 10 mL water (approximately 1 tablespoon) per 25 mg dispersible tablet to the glass or cup to ensure any remaining suspension is dispersed, and administer the resulting suspension immediately.

Delamanid 50 mg tablets

Tablets are film-coated and are not scored.

Tablets, whether taken whole or dissolved in water, are palatable, which increases acceptability for children.

Administration of doses ≥50 mg

- Tablets are intended to be swallowed whole.
- If children have challenges swallowing tablets whole and the 25 mg dispersible tablet formulation is not available, the 50 mg tablet can be administered after dissolving in water:
  - Allow the 50 mg tablets to dissolve over 5–6 minutes in 10 mL water. Doses of 50 mg and over can be administered directly. However, a small volume (5–15 mL) of sugar syrup (ready-made or prepared from food-grade sugar[1]) may be added, if available, to improve the taste and texture and increase acceptability for children.
  - The container should be rinsed with an additional 5 mL clean water and administered to ensure any medicine remaining in the container is taken.
- Although crushing delamanid 50 mg tablets is not ideal, it may make it easier for some children to take the medicine. If the tablets are crushed, it is recommended to disperse them in yoghurt or another soft food (e.g. mashed banana or peanut butter) to improve ease of administration and swallowing. The impact of this manipulation on the amount of medicine absorbed by the body is unknown.

Administration of doses <50 mg

- Dissolve the 50 mg tablet in water and sugar syrup:
  - Allow the 50 mg tablets to dissolve over 5–6 minutes in 5 mL water. Add 5 mL sugar syrup (ready-made or prepared from food-grade sugar[1]) to make a total volume of 10 mL.
  - Administer the volume corresponding to the required dose with a syringe.
- Although not ideal, alternatively the tablet can be split in half with a pill cutter and:
  - dissolved in water and administered (ensuring the container is rinsed with clean water to administer the full dose); or
  - crushed and administered with yoghurt or other soft food.

It is possible to prepare sugar-containing and sugar-free **extemporaneous liquid formulations** of delamanid that permit dose titration for children and for people who cannot swallow whole tablets. These use easily accessible ingredients and equipment and can be conveniently 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 *(11)*.

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] If ready-made sugar syrup is not available, a solution of sugar and water can be prepared by dissolving 28 g (30 mL measured by volume) food-grade sugar (sucrose) into 15 mL hot distilled clean water and then mixing well until the sugar has dissolved. Wait for the syrup to cool to ambient room temperature before administration. (See also Annex 1: "Preparing simple syrup (65% w/w) from sugar (sucrose").) Preparing a larger batch of sugar syrup (e.g. weekly) for use as needed is possible.

For parents and caregivers administering delamanid to children at home

- 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 alcohol- or bleach-based cleaning solution.
- Ensure delamanid 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 delamanid are nausea and vomiting, dizziness, paraesthesia, anxiety, QTc prolongation and night terrors associated with sleep disturbances.

Occasional nightmares may be common in children and are not themselves an indication to stop delamanid. Ongoing nightmares that disturb sleep should prompt review by a clinician. A careful risk/benefit assessment should be undertaken, considering that children on delamanid may have serious forms of MDR/RR-TB, with limited treatment options available.

Monitoring for neuropsychiatric adverse events, including night terrors, is important in children being treated with medicines with known neuropsychiatric side-effects. This is particularly critical when delamanid is administered with cycloserine. These events should be reported through the national pharmacovigilance system.

People receiving delamanid in combination with other potentially QT-prolonging medicines (e.g. clofazimine, bedaquiline 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 *(8)*.

Monthly monitoring of body weight is especially important in children and adolescents. The dose of delamanid 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 and nutrition counselling and support is a crucial part of effective care for people children and adolescents with MDR/RR-TB and their families *(12)*. Information on adherence counselling and support and clinical monitoring for children and adolescents treated with delamanid and other second-line TB medicines can be found in the WHO Operational Handbook on Tuberculosis. Module 5: Management of Tuberculosis in Children and Adolescents *(6)* and Module 4: Treatment – Drug-resistant Tuberculosis Treatment *(8)*.

QTcF (Fridericia's formula) is a formula calculated based on the QT interval on the ECG that 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 delamanid (5 mg/mL) using a 50 mg tablet

Materials

Preparing a modified starch[2] sugar-free vehicle

1. Measure 236 mL of 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 delamanid sugar-free formulation

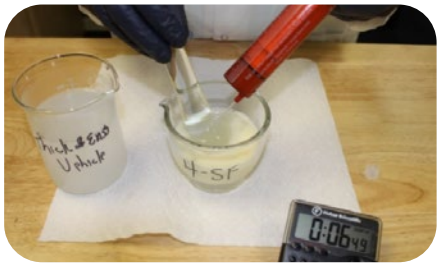
4. Add 10 tablets (50 mg each) to a mortar and pestle.

5. Add 100 mg methyl paraben, 100 mg potassium sorbate, 125 mg citric acid and 125 mg sodium saccharin to the tablets in the mortar.

6. Add 50 mL of distilled water to the mortar using an oral syringe. Let the mixture sit for 5 minutes.

7. Mix the completely disintegrated tablets using a pestle to form a uniform mixture.

8. Using an oral syringe, add an additional 47 mL modified starch[2] sugar-free vehicle to the mortar and mix to form a uniform suspension.



9. Transfer the final contents with total volume 100 mL from the mortar into an amber bottle. The sugar-free extemporaneous suspension 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. Sugar and sugar-free liquid formulations of delamanid for patients with rifampicin-resistant TB. Int J Tuberc Lung Dis. 2023;27(1):13–18).

Annex 2. Preparation of sugar-containing extemporaneous suspension of delamanid (5 mg/mL) using a 50 mg tablet

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 the 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 delamanid suspension in simple sugar-containing syrup

4. Grind 10 tablets (50 mg each) to a fine powder with a mortar and pestle.

5. Mix the powder with a small amount (20 mL added using an oral syringe) of simple syrup prepared in Steps 1–3 above to form a uniform paste. Alternatively, commercially available simple syrup can be used.

6. Add the sugar syrup in increasing amounts while mixing thoroughly until the total combined amount of vehicle added is 97 mL.

7. Transfer the final contents with a 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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