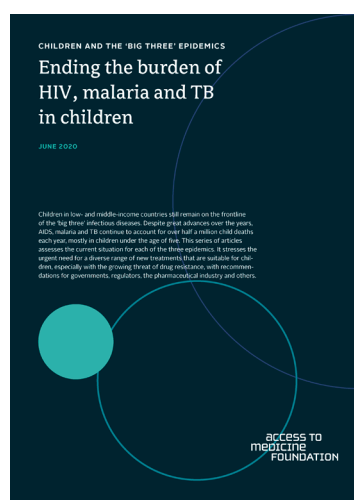


## CHILDREN AND THE 'BIG THREE' EPIDEMICS

# Tuberculosis in children: underdiagnosed and undertreated

JUNE 2020



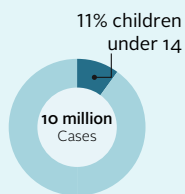
This article is one of a series of three. It dives into the current situation for TB, specifically multidrug-resistant TB (MDR-TB), highlighting the specific burden on children, setting out what needs to happen next in terms of product development and the remaining product gaps. As only a few child-friendly medicines are available for MDR-TB, it underscores the need for a diverse range of new treatments that are suitable for children.

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# Tuberculosis in children: underdiagnosed and undertreated

## AT A GLANCE



**1.1 million children are infected each year**

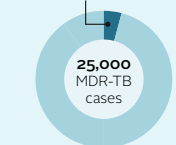
11% of all TB cases are children under the age of 14.



**Children under 5 are most at risk**

Up to 80% of child-TB deaths are children under the age of five.

**4% get diagnosed and treated**



**Multidrug-resistant TB is hugely undertreated**

Only 3-4% of MDR-TB cases in children are diagnosed and treated, resulting in thousands of deaths annually.

Tuberculosis (TB) is currently the leading cause of death from a single infectious agent and is one of the top ten causes of death globally.<sup>1</sup> In 2018, an estimated 10 million cases were reported and a total of 1.5 million deaths occurred. Children represent an estimated 11% of all TB cases, as at least 11 million children under the age of 14 have TB each year.<sup>1</sup> Almost 80% of these cases occur in the 30 ‘High Burden Countries (HBCs)’ – countries that have been acknowledged as shouldering the greatest share of the global TB burden.<sup>1</sup>

Studies have estimated that 80% of children who died from TB were under the age of five – making TB one of the top 10 causes of paediatric deaths.<sup>2</sup>

### The threat of drug-resistance

Compounding these alarming numbers is the challenge of drug resistance – specifically, multi-drug resistant tuberculosis (MDR-TB). MDR-TB is a form of TB which does not respond to the recommended first-line treatments, isoniazid and rifampicin – the two most potent TB treatments. Further, extensive drug resistant TB (XDR-TB) is a type of MDR-TB that is also resistant to three or more second-line treatments. Drug-susceptible TB, however, means that TB can be effectively treated with the first-line treatment regimen when used appropriately. Each year, approximately 25,000 children fall ill with MDR-TB. Of these, only 3-4% are diagnosed and treated and consequently approximately 21% of children with MDR-TB likely die.<sup>3</sup>

### Few incentives, few options

Despite the significant burden of MDR-TB among children, the market size is small with little commercial incentive, exacerbated by the uncertainties over patient numbers and the inability to correctly diagnose children in resource limited settings. This low-volume/low-profit market has proven to be a disincentive for pharmaceutical companies to invest in developing TB treatments, let alone

treatments for MDR-TB. What's more, additional clinical studies and even further investments are needed to establish safety in children and develop appropriate child formulations.<sup>4</sup> In turn, few paediatric treatments for MDR-TB exist, leaving many children continually at risk as they turn to adult formulations for treatment. Yet even for the treatment of adults, the success rate with the existing treatment regimens is low.<sup>1</sup>

When parents and healthcare providers have to resort to manipulating or administering adult formulations, this increases the risk of inadequate dosing, and the subsequent probability of developing resistance. Splitting TB pills also removes coatings which mask bitterness, making palatability and therefore administration very difficult. Further, MDR-TB regimens require approximately seven different types of pills and/or liquids combined, sometimes with different modes of administration, as well as lengthy treatment regimens that can last as long as 18 months, creating additional adherence challenges.<sup>5</sup>

### A MAJOR CHALLENGE IN CHILDHOOD TB MANAGEMENT IS DIAGNOSIS

With existing diagnostic tools, it is difficult to determine whether a child has drug-resistant TB. Children usually cannot spontaneously produce sputum – the specimen needed for analysis – to confirm TB infection through a bacteriological test, also referred to as the diagnostic ‘gold standard’.

Only 30% of diagnosed children are confirmed through this approach.<sup>6</sup> Consequently, the diagnosis of TB in children relies mostly on non-specific clinical symptoms, supported by evidence from TB contacts and radiographs of the chest. Existing diagnostic tests for TB in children have shortcomings and are often unavailable in high-burden countries where children often access general (child) health services where capacity to recognise and diagnose TB is limited. The development of affordable, reliable diagnostic tests for children in low-resource settings will be a crucial step in combating TB.

**A unified approach**

Under such market conditions, it is unlikely that this issue will change. High-levels of intervention are needed to establish clear priorities and incentives that can help foster the development of treatments and their availability. With such measures, companies are more likely to take action. Coordination with governments, multilateral organisations like the World Health Organization (WHO), donors, regulators and the pharmaceutical industry is required for this to happen.

**The role for pharma companies**

Pharmaceutical companies have a role to play in enabling the availability and accessibility of child-friendly formulations for the prevention and treatment of MDR-TB. Existing MDR-TB treatment regimens are limited in their effectiveness, showing a need to develop new, more effective MDR-TB treatments for both the adult and paediatric populations. The availability of new and existing treatments for younger children who are not yet eligible for the adult dosage and formulation must be ensured.

Effective MDR-TB treatments that are easy to administer and palatable are specifically needed so adherence in children can be facilitated. Solid oral formulations such as granules, pellets, dispersible, heat stable, chewable, taste-masked, and scored tablets can help overcome the current challenges associated with adherence issues. Notably, MDR-TB treatment require a combination of various medicines, some of which are under patent by different companies. In order to develop safe and effective treatments, R&D collaboration among companies and investment is needed, alongside clear recommendations on dosing.

**TUBERCULOSIS - MARKET INSIGHT**

# What TB treatments are on the market that are suitable for children?

According to WHO guidelines, children with drug-susceptible TB (DS-TB) should be treated with a regimen of a combination of TB treatments including isoniazid, rifampicin, pyrazinamide. In settings with high prevalence of HIV, treatments should also include ethambutol.<sup>7</sup> The dosing of these treatments depends on the body weight of the child. In 2010, WHO updated its dosing guideline for paediatric DS-TB treatments, but until recently there were no existing formulations that matched the new dose recommendations.<sup>8</sup> Currently, few companies are marketing paediatric treatment options for DS-TB, in both a single and FDC formulation, that correspond to these updated guidelines. Yet, paediatric treatments for DS-TB do exist, serving a large proportion of the market and are outlined in table 8.

For multidrug resistant (MDR-TB), there are no established treatment guidelines due to the lack of available data and regimens with high success rates. However, for both adults and children, WHO recommends a combination of multiple TB-treatments, including novel treatments such as Johnson & Johnson's bedaquiline (Sirturo®), Otsuka's delamanid (Delyba™) and pretomanid (only recommended for XDR-TB under operational research settings\*) developed by the TB Alliance and marketed by Mylan.<sup>5</sup> Of these three, bedaquiline (Sirturo®) and delamanid (Delyba™) are approved for the use in children, as displayed in table 8.

**Two products for MDR-TB offer a lower risk of resistance**  
There are multiple paediatric FDCs and single treatment options for DS-TB that come in accurate dosing and appropriate formulations when compared to MDR-TB. Yet, there are still gaps in optimal DS-TB treatment options for children weighing less than 5kg.

When it comes to MDR-TB treatments, Johnson & Johnson's bedaquiline (Sirturo®) and Otsuka's delamanid (Delyba™) are the only two novel treatments approved in the last 50 years for the treatment of MDR-TB in patients under the age of 18. They have been conditionally approved for use in children above the age of five and six, respectively. These novel treatments offer the chance to remain effective for longer if used responsibly, because the compounds are not related to existing first-line agents, minimising the risk of cross-resistance. Bedaquiline (Sirturo®) is the only treatment available in a formulation that is suitable for young children and children who cannot swallow pills.

\* Revised guidelines expected shortly

**TABLE 8 Which companies are making child-friendly TB treatments available on the market?**

This table looks at some examples of companies that are making treatments for DS-TB and MDR-TB available on the market, looking at a selection of formulations available for children. The table does not include all MDR-TB treatment options on the market but specifically looks at the most recent novel TB treatments, as they are the most promising in addressing MDR-TB. In the case of DS-TB, the table highlights treatments that take into account specific paediatric needs, such as dispersible tablets and FDCs, as these are more likely to tackle adherence issues across age and weight bands. While not mentioned in the table, these treatments are also available in higher dosage and non-dispersible forms that can also be used for certain ages in the paediatric population.

Companies	Treatment	Formulation
	DS-TB	
Lupin; Macleods	isoniazid/rifampicin	50/75mg fixed-dose combination dispersible tablet
Macleods	isoniazid/pyrazinamide/rifampicin	50/150/75mg fixed-dose combination dispersible tablet
Micro Labs	isoniazid	50mg; 100mg dispersible tablet
Macleods	ethambutol	100mg dispersible tablet
Macleods; Micro Labs	pyrazinamide	150mg dispersible tablet
	MDR/XDR-TB	
Johnson & Johnson	bedaquiline (Sirturo®)	20mg dispersible tablet
Otsuka	delamanid (Delyba™)	50mg tablet

The recommended TB treatments are available for children weighing >5kg in a fixed-dose combination dispersible tablet

Bedaquiline (Sirturo®) and delamanid (Delyba®) are approved for children over the age of 5 and 6, respectively, for the treatment of MDR-TB. WHO guidelines recommend the use of delamanid (Delyba®) for children over the age of 3.

TUBERCULOSIS - R&D INSIGHT

# Which companies are developing TB treatments for children?

As current TB treatments become less effective due to resistance, the need to develop new treatments grows more pressing. While progress has been made in the development of new TB treatments for adults such as such bedaquiline (Sirturo®), pretomanid and delamanid (Delyba™), children are often overlooked in this area. To help accelerate the development of appropriate paediatric formulations and reach an evidence-based consensus regarding priority TB treatments, the first WHO-led Paediatric Antituberculosis Drug Optimization Meeting (PADO-TB 1) was held in February 2019. The meeting was convened to build on the experience of the HIV PADO meetings and address the UN General Assembly High Level Meeting on TB targets for treatment and prevention in children, which was held in 2018.<sup>9</sup> Representatives from high-burden countries and experts from the Global Fund, Unitaid, WHO, MPP, CHAI, the Union, Médecins Sans Frontières (MSF), Global Drug Facility (GDF) and various academic institutions, amongst others, decided on a list of short and long-term priority areas for drug development for children. This section looks at which paediatric products are currently in development, if the industry is actively addressing the identified PADO-TB 1 priorities and how they are addressing future accessibility.

### PRIORITISING UNMET NEEDS - PADO PRIORITIES

The WHO-led PADO group identifies priorities for the development of paediatric anti-TB drugs and formulations.†

Short-term (all dispersible scored)	Watch-List
<b>DS-TB</b>	<b>DS- TB</b>
<ul style="list-style-type: none"> <li>Rifampicin</li> <li>Rifapentine</li> </ul>	<ul style="list-style-type: none"> <li>Isoniazid/pyrazinamide/rifampicin/levofloxacin FDC</li> <li>Isoniazid/pyrazinamide/rifampicin/ethambutol FDC</li> </ul>
<b>MDR-TB</b>	<b>MDR-TB</b>
<ul style="list-style-type: none"> <li>Bedaquiline †</li> <li>Clofazimine</li> <li>Delamanid</li> <li>Linezolid</li> <li>Pretomanid</li> </ul>	<ul style="list-style-type: none"> <li>Telacebec (Q203)</li> <li>Sutezolid (PNU-100480)</li> <li>Delpazolid (LCB01-0371)</li> <li>Moxifloxacin - taste masked</li> </ul>

† Preventative treatments are not included.

FIGURE 7 Three projects in the TB paediatric pipeline target PADO priorities\*

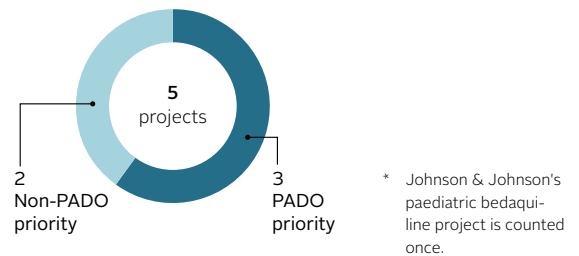


TABLE 9 What is in the paediatric TB pipeline?

The table below provides a breakdown of companies that are developing paediatric DS-TB and MDR-TB medicines and identifies those that are listed on the PADO priority list.\*

Company	Phase I	Phase II	Phase III	Approval	Other
Johnson & Johnson**		Bedaquiline (Sirturo®) - MDR-TB - Age: 2-5 years - Dispersible tablet - ☐			
		Bedaquiline (Sirturo®) - MDR-TB - Age: 0-2 years - Dispersible tablet - ☐ ***			
Macleods					Linezolid – MDR-TB - Age: Paediatric, specific age unknown - 150mg Dispersible tablets - ☐
					Isoniazid – MDR-TB - Age: Paediatric, specific age unknown - 100 mg Dispersible tablets
Otsuka		Delamanid (Delyba™) - MDR-TB - Age: 0-6 years - 25mg Dispersible tablet - ☐			
Sanofi		Rifapentine/isoniazid paediatric – Preventative treatment - Age: Paediatric, specific age unknown - FDC dispersible formulation			

☐ Listed on the PADO-TB 1 priority list

\* This is not an exhaustive presentation of the TB pipeline.  
 \*\* Johnson & Johnson has one phase II project to establish the safety, tolerability and pharmacokinetic profile of bedaquiline in combination with other second-line agents for the treatment of TB in children/adolescents. This study consists of four cohorts. Two cohorts of 12-18 years and 5-12 years, were approved in 2019 and 2020, respectively.

\*\*\* Phase II study, cohort not yet enrolled.

† Bedaquiline (Sirturo®) developed by Johnson & Johnson was approved by the FDA in May 2020.

### Few projects aimed at children in the pipeline

Overall, the pipeline for paediatric TB treatments is small, including five child-friendly formulations of existing TB medicines, three of which target MDR-TB. Of these five projects, one project is to establish accurate dosages of bedaquiline (Sirturo®) across different age groups for the treatment of MDR-TB. Three projects are identified as PADO-TB 1 priorities including the two paediatric bedaquiline (Sirturo®) projects by Johnson & Johnson; paediatric delamanid (Delyba™) by Otsuka; and paediatric linezolid by Macleods. Otsuka is expecting approval by the European Medicines Agency (EMA) for the expanded paediatric indication of delamanid (Delyba™) in the second half of 2020 and approval of the 25mg dispersible tablet in 2021. Further, the TB Alliance completed a Phase I pharmacokinetics study of pretomanid in 2020 and plans to start dosing paediatric patients in 2021.

### Novel paediatric projects

There are two projects in development that are paediatric adaptations of novel TB medicines, bedaquiline (Sirturo®) and delamanid (Delyba™) which are also listed on the PADO-TB 1 priority list. In addition, four companies (LegoChem, Otsuka, Qurient and Sequella) are currently developing four novel late-stage projects targeting MDR-TB in adults that are also identified on the PADO-TB 1 priority list.<sup>13</sup> Once these products have been approved for sale by the relevant regulatory authority, regulatory obligations will require the companies to study the product in children. However, significant delays often occur between the approval of the adult formulation and children formulations, partially due to waivers or deferral requests by companies and lack of incentives to begin the process prior to approval. Companies should start ahead and refrain from submitting deferrals in order to shorten such delays.

These novel late-stage projects are:

- Otsuka: OPC-167832
- Sequella Inc., & TB-Alliance: Sutezolid (PNU-100480)
- Qurient Co., Ltd: Telacebec (Q203)
- LegoChem Biosciences, Inc: Delpazolid (LCB01-0371)

### WHAT VACCINES ARE IN THE PIPELINE?

A total of 14 vaccines are in clinical development for the prevention of TB.<sup>10</sup> Of these 14, two are being developed for neonates and infants and one paediatric vaccine project is in pre-clinical development. Pharmaceutical companies are involved in seven of the 14 vaccine projects in clinical development. One example of a vaccine in development (albeit not yet designed for use in children) is the TB prophylactic vaccine M72/AS01 being developed by GSK. In January 2020, GSK announced that it will license the vaccine to the Bill & Melinda Gates Medical Research Institute for the development and potential use of M72/AS01 in low-income countries affected with a high burden of TB.

## TUBERCULOSIS - ENSURING ACCESS

# How are companies ensuring access to their current and future treatments for children?

Some of the companies in the pipeline are taking steps to ensure their TB products will be accessible once approved. For example, GSK has licensed its tuberculosis vaccine candidate to the Bill & Melinda Gates Medical Research Institute for continued development. Collaborating with partners that have a clear access agenda is one way to ensure wide access upon approval. Further, Johnson & Johnson has committed to file paediatric bedaquiline (Sirturo®) for registration in the countries where it conducts clinical trials, upon approval.

TABLE 10 What access strategies are companies deploying?

This table provides examples of access strategies that companies and partners apply to their paediatric TB products on the market or projects in the pipeline.

Access strategies	Example of company practice
Registration	Johnson & Johnson registered bedaquiline (Sirturo®) 100mg in 28 low- and middle-income countries.
Affordability	Developed by the TB Alliance and commercialised by Macleods, the FDCs isoniazid/pyrazinamide/rifampicin and isoniazid/rifampicin dispersible tablets were introduced at an average price of USD 15.54 for a full six-month treatment course, which falls below the median price of older paediatric treatments.
Ensuring adequate supply	Since its 2016 agreement with Global Drug Facility (GDF), Otsuka has supplied delamanid (Delyba™) to 89 countries, including 30 with a high burden of multidrug-resistant TB (MDR-TB).
Voluntary licence	In 2019, Otsuka and Mylan announced a licence agreement to commercialise delamanid (Delyba™) for MDR-TB in High-Burden Countries. Otsuka is currently in the process of a technology transfer to Mylan to enable generic manufacturing of delamanid.
WHO-Prequalification	All products displayed in table 8 are WHO-prequalified and/or approved by the Expert Review Panel of the Global Fund, allowing for UN and Global Fund procurement and accelerating the registration process in countries with weak national regulatory authorities.
Access through partnerships	Through the STEP-TB project, the FDCs isoniazid/pyrazinamide/rifampicin and isoniazid/rifampicin dispersible tablets were developed by the TB Alliance and commercialised by Macleods and Lupin. Beyond drug development, the project focused on procurement and regulatory pathways to help ensure the product's accessibility.

## TUBERCULOSIS - CASE STUDIES

# How companies and organisations are working to develop optimal paediatric TB treatments

### Addressing the unmet need for new paediatric TB treatments

MACLEODS, LUPIN, TB ALLIANCE, UNITAID, USAID, WHO

**What:** Unitaid and USAID in partnership with TB Alliance, the WHO Global TB Programme, and the Department of Essential Medicines and Health Products, launched the STEP-TB project to overcome obstacles in DS-TB paediatric drug-development.

**Context:** Commercial incentives underpinning the TB market are weak, yet new mechanisms can help encourage the development and availability of treatments.

### The need for new paediatric TB formulations

Until recently, paediatric TB programmes were largely dependent on older treatment methods geared mainly towards adults that involved the use of bitter-tasting pills or dispersible tablets in outdated, incorrect dosages.<sup>8</sup> Often, healthcare practitioners and caregivers would need to break or crush the pills and estimate the correct dosage for their paediatric patients, usually resulting in imprecise dosing.

### Developing pathways for childhood TB treatments

To help catalyse the development of new treatments and address the lack of access to existing products, Unitaid in partnership with TB alliance and WHO, launched the Speeding Treatments to End Paediatric Tuberculosis (STEP-TB) project in August 2013. The programme, with an initial investment of USD 16.7 million, received additional support from USAID.<sup>8</sup>

Building on existing treatment guidelines, STEP-TB successfully identified two pharmaceutical companies, Lupin and Macleods, to develop and commercialise two fixed-dosed combination treatments for paediatric DS-TB (isoniazid/pyrazinamide /rifampicin 50/150/75mg and isoniazid/rifampicin 50/75mg) and gain WHO prequalification. Conditions included manufacturing at production scale and ensuring affordability through a global mechanism. What helped achieve this was the absence of patents and established safety of the individual treatments, allowing for the development of a fixed-dose combination. Additionally, TB Alliance offered its expertise throughout the product development and commercialisation process and helped to identify the current and future demand as part of the programme.

### Market impact

By identifying market barriers and engaging in innovative industry collaborations, STEP-TB aimed to provide manufacturers with an incentive to develop properly dosed

and affordable paediatric medicines.<sup>8</sup> Macleods was the first pharmaceutical company that brought the two fixed-dosed combinations to the market and through WHO Prequalification, in 2015 and 2017, respectively. Since then, Lupin has also begun manufacturing and selling isoniazid/rifampicin, having received a positive opinion of the Global Fund ERP and is currently pending WHO Prequalification. In total, more than one million courses of these products have been ordered in 88 countries.

### Finding the right MDR-TB treatment for children

STELLENBOSCH UNIVERSITY, TB ALLIANCE, UNITAID

**What:** BENEFIT Kids project was developed through a grant from Unitaid to Stellenbosch University to produce and evaluate child-friendly treatments for MDR-TB

**Context:** Address the absence of optimal treatment options for MDR-TB in children

### What is BENEFIT Kids?

In 2019, Unitaid granted Stellenbosch University USD 18.9 million to develop and evaluate child-friendly treatments for MDR-TB and assess regimens for the prevention of the disease. The project, "Better Evidence and Formulations for Improved MDR-TB Treatment for Children" (BENEFIT Kids) will run until October 2022.<sup>11</sup>

### How are they enabling future access?

The BENEFIT Kids project is comprised of three components. Firstly, it aims to strengthen the evidence of optimal dosing, safety, efficacy, acceptability and costs of medications for treatment and prevention of MDR-TB in children. Initially, the project will study adjusted formulations of several key MDR treatments to enable clinicians and national programmes to better treat children in the short term. New or improved generic formulations of three treatments will also be developed: linezolid, bedaquiline, and moxifloxacin. This is an important step in creating policies that can impact clinical care. Secondly, it will develop child-friendly formulations for MDR-TB treatment and preventive therapy, taking into consideration the specific needs of children. Thirdly, the project will engage in market shaping activities in order to ensure effective and sustainable roll-out.<sup>11</sup>



### Developing paediatric bedaquiline (Sirturo®) for a wider range of children with MDR-TB

GLOBAL DRUG FACILITY, JOHNSON & JOHNSON

**What:** Johnson & Johnson is developing a paediatric formulation of bedaquiline (Sirturo®) and aims to build on existing access and stewardship plans that are currently in place for the adult formulation.

**Context:** Bedaquiline (Sirturo®) is currently approved for children above the age of five, with a 20mg dispersible tablet approved in May 2020.

Johnson & Johnson's breakthrough medicine bedaquiline (Sirturo®) was conditionally approved by the US FDA in December 2012 through fast-track accelerated approval as the first innovative treatment for multi-drug resistant tuberculosis in 40 years. In 2019, bedaquiline (Sirturo®) was approved by the FDA as part of a combination therapy for eligible MDR-TB patients aged 12 years and above. In May 2020, the FDA approved bedaquiline (Sirturo®) 20mg dispersible tablet for children above the age of five. This approval marked the first lower-dose and child-friendly formulation of bedaquiline (Sirturo®) since its approval in 2012.

### Developing bedaquiline (Sirturo®) for children across all ages and weight bands

Currently, Johnson & Johnson is developing bedaquiline (Sirturo®) for use across a wider range of age and weight bands. In addition to the newly approved paediatric formulation of bedaquiline (Sirturo®) in the form of a 20mg dispersible tablet for children aged five to 12, a clinical study is currently on-going to evaluate the dispersible formulation and paediatric dosing in children aged two to four years old. Once data is available, Johnson & Johnson has committed to enrol children from zero to two years old.

### Expanding existing access and stewardship plans to paediatric bedaquiline (Sirturo®)

By planning ahead while a product is in clinical development – pharmaceutical companies can provide swifter access to new products at affordable prices and have measures in place from day one to ensure new products are used prudently (known as stewardship).

Johnson & Johnson aims to ensure the availability and accessibility of bedaquiline (Sirturo®) through a number of routes: equitable tiered pricing; purchasing via the Global Drug Facility; and through institutional purchasing by international NGOs. The lower tiered price for treatment is available

at a price of USD 400 for a six-month course.<sup>12</sup> The company has committed to build on its existing access pathways that are currently in place for the adult formulation of bedaquiline and apply these to the paediatric formulations upon approval, including ensuring accessibility through the Global Drug Facility. Further, to promote the likelihood of the product being used appropriately and remaining effective over time, current stewardship initiatives will also be expanded to the paediatric formulations.

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