



# DR-TB DRUGS UNDER THE MICROSCOPE

6<sup>TH</sup> EDITION

## 5 URGENT ACTIONS TO IMPROVE DR-TB TREATMENT

1. Switch to the new DR-TB treatment guidelines
2. Make bedaquiline and delamanid affordable
3. Overcome prohibitive patents and licenses
4. Adopt effective national drug procurement policies
5. Support public health-driven R&D

### INTRODUCTION

Drug resistance is a major public health crisis thwarting the effective treatment and care of people living with tuberculosis (TB) – the world's leading infectious disease killer. Declared a global health emergency by the World Health Organization (WHO) in 2014 and again in 2017, drug-resistant TB (DR-TB) affected an estimated half million people in 2018 yet only 1 in 3 started treatment.<sup>1</sup>

Until recently, the standard DR-TB treatment regimens recommended by WHO – and still in use by many countries –

have a high pill burden, long treatment duration (up to two years), painful daily injections, severe side effects and poor treatment outcomes. These regimens cured only 56% of people with multidrug-resistant TB (MDR-TB), and 39% of people with extensively drug-resistant TB (XDR-TB).<sup>a,1</sup>

In March 2019, WHO released new DR-TB treatment guidelines,<sup>2</sup> recommending more effective and easier-to-take all-oral drug regimens. In July 2019, WHO Director-General Dr Tedros Adhanom

Ghebreyesus called for countries to transition to all-oral DR-TB regimens by World TB Day, 24 March 2020.<sup>3</sup> By this time, 100% of people newly enrolled on treatment should be offered these optimal regimens.

This Issue Brief examines the current landscape of DR-TB drug pricing and access policies, and what needs to be done by governments, policymakers and health care providers to get these lifesaving medicines to the people who need them most.



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Mr Mncwabe is being treated for DR-TB at Doris Goodwin Hospital in Pietermaritzburg, KwaZulu-Natal, South Africa. He is enrolled in the TB PRACTECAL clinical trial, a study being conducted by MSF to evaluate shorter, safer 6-month DR-TB treatment regimens, including those using the newer TB drugs bedaquiline and pretomanid.

### STATE OF DRUG-RESISTANT TB

#### In 2018:

- An estimated half million people fell ill with MDR/RR-TB<sup>a</sup>
- 39% of people with MDR/RR-TB were diagnosed
- Only 1 in 3 people with MDR/RR-TB were started on treatment
- 56% and 39% of people treated for MDR/RR-TB and XDR-TB<sup>a</sup> were successfully cured, respectively
- Three countries accounted for half of the world's cases of MDR/RR-TB: India (27%), China (14%) and the Russian Federation (9%)

Source: WHO Global TB Report 2019

<sup>a</sup> MDR-TB is defined as TB resistant to isoniazid and rifampicin, with or without resistance to other first-line drugs. RR-TB is rifampicin-resistant TB. XDR-TB is defined as resistance to at least isoniazid and rifampicin, any fluoroquinolone and any of the three second-line injectable agents (amikacin, capreomycin or kanamycin).

#### MSF Access Campaign

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## EXECUTIVE SUMMARY

To accelerate access to DR-TB treatment and increase cure rates, Médecins Sans Frontières (MSF) recommends five urgent actions: adopting new treatment guidelines, lowering the price of breakthrough drugs, surmounting prohibitive patents and licensing policies, using effective drug procurement practices, and supporting public health-driven research and development (R&D).<sup>b</sup>

Based on the new 2019 WHO treatment guidelines for MDR- and XDR-TB, MSF urges **countries to make a timely switch to the newly recommended all-oral drug regimens**, discontinuing the use of harmful and difficult-to-use injectable agents (kanamycin and capreomycin), and prioritising the use of the breakthrough newer drug bedaquiline.

But to actually be able to give bedaquiline to more people with DR-TB, it needs to be more affordable. The current price of bedaquiline is too expensive for many countries with a high DR-TB burden. This is why **MSF is calling on Johnson and Johnson (J&J) to reduce the price of bedaquiline to no more than US\$1 a day**, especially given the fact that substantial public and philanthropic funding went into the development of bedaquiline. This overall collective effort in drug R&D for bedaquiline needs to be reflected in its availability for people with DR-TB for whom access to this medicine is a matter of life or death.

**High drug prices are not just a barrier to access bedaquiline, but also for other increasingly vital DR-TB drugs, such as delamanid.** On top of high prices, **restrictive patents and exclusive licensing of bedaquiline and delamanid**, as well as lack of transparency around the pricing

and licensing terms of the newest DR-TB drug pretomanid, pose threats to treatment access.

As for country-level policies, national drug registration is essential, as not all DR-TB medicines are yet registered in all high-burden TB countries. And as donor support stagnates, including contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria, **countries are more rapidly shifting from Global Fund-supported pooled procurement mechanisms to domestically funded national processes for the purchase of medicines. Governments need to ensure (i) medicine affordability**, by allowing the use of international pooling mechanisms, being transparent on purchase pricing, utilising pro-access legal safeguards (i.e., TRIPS), and removing tariffs; **(ii) medicine quality**, by recognising WHO Prequalification or Stringent Regulatory Authority (SRA) approval in national tenders; and **(iii) medicine supply**, by joining the WHO Collaborative Registration Procedure (CRP), expediting registration of WHO-prequalified or SRA-approved drugs, and using import waivers for unregistered drugs.

Finally, **we must change the way R&D is done** to ensure affordable and sustainable access to new public health tools for people in need wherever they live. We need an R&D ecosystem focused on improving health outcomes, rather than maximising profit. We need governments to support innovative funding that is not market-based; open-source and collaborative research, including data and molecule sharing; transparent and non-exclusive licensing; transparency of development costs and real prices; and translation of shared efforts in medical R&D into joint decision-making over the use of and access to health tools.

# 5 URGENT ACTIONS TO IMPROVE DR-TB TREATMENT

## 1. COUNTRIES MAKING THE SWITCH

### New DR-TB full-course treatment recommendations

The new 2019 WHO guidelines<sup>2</sup> prioritise the use of all-oral long regimens for the treatment of MDR-TB and XDR-TB, including the newer drug bedaquiline. They recommend against the use of two of the main injectable agents commonly used before, which have worse outcomes and can cause severe side effects such as deafness.

#### Which medicines to use?

An MDR-TB or XDR-TB regimen should consist of all three medicines in Group A, and one or both medicines in Group B (Table 1). Group C drugs should be added, as needed, including as substitutes for Group A or B drugs when they cannot be used due to resistance or intolerance.

- The core drugs are levofloxacin/moxifloxacin, linezolid and bedaquiline in Group A, and clofazimine and cycloserine in Group B.
- The injectables kanamycin and capreomycin should not be used. Amikacin and streptomycin should only be used if there

is confirmed susceptibility and if monitoring for hearing loss can be ensured.

- Delamanid remains a Group C drug to be used when Group A or B medicines cannot be used.
- In children, bedaquiline is approved for patients 6-17 years old; delamanid is approved for children 3 and older.

#### How many drugs and for how long?

- Treatment should start with at least four effective drugs for the initial 6 months, and at least three effective drugs thereafter. The total duration is 18 to 20 months (including 15 to 17 months after culture conversion).
- Five drugs should be given if (i) more than one drug is expected to cease after 6 months, (ii) drug susceptibility testing (DST) is unavailable and local prevalence of resistance to one of the drugs is known to be high, or (iii) agents included in the regimen are unlikely to cure the patient (i.e., if there are not enough drugs from Groups A or B).

<sup>b</sup> This report focuses on treatment-related actions for DR-TB care. Governments must also take all necessary steps to scale up TB diagnosis, given the deadly testing gap and the persistent problem of underdiagnosing people with TB and DR-TB.

**TABLE 1: GROUPS OF DRUGS IN THE NEW LONG REGIMENS**

Groups & Steps	Medicine
Group A: Include all three medicines	Levofloxacin (Lfx) <u>or</u> moxifloxacin (Mfx)
	Bedaquiline (Bdq)
	Linezolid (Lzd)
Group B: Add one or both medicines	Clofazimine (Cfz)
	Cycloserine (Cs) <u>or</u> terizidone (Trd)
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol (E)
	Delamanid (Dlm)
	Pyrazinamide (Z)
	Imipenem/cilastatin (Imp/Cln) <u>or</u> meropenem (Mpm)
	Amikacin (Am) <u>or</u> streptomycin (S)
	Ethionamide (Eto) <u>or</u> prothionamide (Pto)
	<i>p</i> -aminosalicylic acid (PAS)

While the standardised short-course regimen may be offered to selected patients when there is no resistance to any of the drugs (except for isoniazid), WHO encourages exploration of all-oral short regimens under operational research conditions. The drugs that should be prioritised as part of short all-oral regimens are bedaquiline, levofloxacin, linezolid, clofazimine and delamanid.<sup>4</sup>

### Evidence in support

A meta-analysis of 12,030 patients from 25 countries<sup>5</sup> showed reduced mortality and increased treatment success for patients receiving linezolid, levofloxacin, moxifloxacin or bedaquiline, while regimens with kanamycin and capreomycin were associated with worse outcomes. Results from Belarus showed MDR-TB treatment outcomes improve from 58% to 93% after introducing bedaquiline,<sup>6</sup> while results from Armenia showed treatment success increase by 30% in fluoroquinolone-resistant patients receiving bedaquiline and linezolid.<sup>7</sup> In South Africa, treatment success increased from 13% to 66% among 272 XDR-TB patients receiving bedaquiline.<sup>8</sup> Furthermore, bedaquiline has the lowest risk of side effects among second-line drugs.<sup>2</sup> MSF is contributing to this body of evidence through operational research in 14 countries, and as part of the endTB project,<sup>9</sup> the largest prospective observational study of bedaquiline and delamanid. More than 2,000 people have been treated with the newer drugs – 1,750 with bedaquiline, 899 with delamanid, and of them 412 with a combination of both medicines – as of September 2019. Modelling studies conducted in South Africa, India and Russia suggest that

replacing injectable aminoglycosides with bedaquiline is more cost-effective while improving treatment success.<sup>10,11</sup>

### Regimen prices

To date, only the standardised shorter DR-TB regimen comes close to the US\$500 target called for by MSF.<sup>12</sup> The prices of longer DR-TB treatment regimens remain relatively expensive (see Annex 2). In 2019, the lowest worldwide price of longer regimens for fluoroquinolone-sensitive patients requiring 6-18 months of bedaquiline is still US\$1,000-2,000 per patient. This is despite significant price decreases gained by the Stop TB Partnership's Global Drug Facility (GDF) for individual DR-TB drugs combined with bedaquiline, which lowered regimen prices by a range of 6-40% from 2018 to 2019.

For people with fluoroquinolone resistance requiring bedaquiline and delamanid for 20 months, regimens are priced at US\$8,000 but increase to US\$12,000 when imipenem-cilastatin is added. These regimen prices decreased less than 10% from 2018 to 2019; the regimen prices remain high mainly due to the high prices of bedaquiline and delamanid.

The 9-month amikacin-based shorter regimen conditionally recommended by 2019 WHO DR-TB guidelines is now at the same price compared to the kanamycin-based regimen, which makes the necessary switch from kanamycin to amikacin feasible budgetarily at country level. However, this regimen is not the WHO-preferred regimen, and the use of an injectable has severe side effects, administration challenges and costs to consider, so this is not a solution to lowering prices of MDR-TB regimens.

## FURTHER IMPROVEMENTS TO DR-TB TREATMENT: CONSIDERATIONS FOR WHO AND TREATMENT PROVIDERS

### 1. Beyond 6 months of bedaquiline and delamanid

Growing evidence supports the safety and efficacy of using bedaquiline and delamanid for more than 6 months. In an MSF-led retrospective analysis of people with DR-TB treated in Armenia and Georgia, 19% of those with culture conversion reverted to culture-positive after stopping bedaquiline at 6 months.<sup>13</sup> In the endTB project, more than half of patients have received more than 24 weeks of bedaquiline or delamanid, and interim analyses have shown no safety concerns in extending treatment. MSF believes that, depending on the tolerability of the treatment regimen, many people with MDR/RR-TB will need bedaquiline and delamanid throughout the full treatment course. WHO will review data on this from endTB and other cohorts in 2019. Meanwhile, MSF urges countries to continue using bedaquiline and delamanid beyond 6 months with systematic data collection, in order to contribute evidence for a prompt update of DR-TB treatment guidelines.

### 2. Delamanid for the treatment of MDR-TB

While delamanid has been classified as a Group C drug, increasing evidence shows that delamanid can play a significant role in improving DR-TB outcomes. In a Phase III study, 88% of people with MDR- and XDR-TB receiving delamanid achieved culture conversion at month 6.<sup>14</sup> In the endTB cohort, where 658 people received delamanid, 79% of patients culture-converted at 6 months, despite significant comorbidities.<sup>15</sup>

### 3. Pretomanid, a new drug added to the arsenal: opportunities and concerns

In August 2019 the US Food and Drug Administration (FDA) approved the use of a new TB drug, pretomanid, when used in combination with bedaquiline, and high-dose linezolid<sup>c</sup> (BPAL regimen) for 6-month (extendable to 9 months) treatment of adult patients with pulmonary XDR-TB, or treatment-intolerant or non-responsive MDR-TB.<sup>16</sup>

FDA approval of BPAL is based on initial promising results from the Nix-TB trial showing 90% (out of 80 patients assessed) with a favourable treatment outcome, despite high rates of side effects, notably peripheral neuropathy (experienced by 81% of the 109 people treated) due to the high dose of linezolid.<sup>17,18</sup> These encouraging results from the Nix-TB trial

are tempered against the relatively small number of patients included, the inability to compare the regimen with modern alternatives, and the lack of data for oft-forgotten groups of patients such as children, pregnant and lactating women and people living with HIV receiving dolutegravir.

Once available, countries could consider BPAL use in targeted settings under close clinical monitoring or operational research conditions, to offer patients a shorter treatment regimen for XDR-TB and to simultaneously gather experience under real-world conditions while waiting for clinical trial results.

A number of clinical trials are looking at regimens with pretomanid, including in combination with lower doses of linezolid, such as TB Alliance's ZeNix trial<sup>19</sup> and MSF's TB PRACTECAL<sup>20</sup> trial. TB PRACTECAL will evaluate the safety and efficacy of 6-month regimens containing bedaquiline, pretomanid and lower doses of linezolid for the treatment of adolescents and adults with MDR- or XDR-TB (final outcomes expected early 2022). In addition, the future role of pretomanid as a treatment option outside of this regimen needs to be explored. As of the end of September, the price of pretomanid has not been announced by the developer of pretomanid, the non-profit product development partnership TB Alliance, nor Mylan, which will be marketing the drug.

### 4. Paediatric DR-TB treatment

The new paediatric pharmacokinetic data on bedaquiline and delamanid allow for increased use of these newer drugs, though paediatric formulations for younger age groups are missing. While delamanid is currently recommended from 3 years of age, the current 50mg formulation marketed for adults can only be used for children 6 years or older. Dispersible tablets of 25mg are only available through compassionate use from Otsuka for children older than 3, while paediatric trials are being finalised and bioavailability studies for delamanid 50mg crushed tablets are under way.<sup>21</sup> Bedaquiline is not currently recommended in children who are younger than 6, leaving this age group with limited treatment options. The newly developed paediatric DR-TB formulations for clofazimine, cycloserine, ethionamide, isoniazid, levofloxacin, moxifloxacin and pyrazinamide have been made available through the GDF (see Annex 3), and are currently being used by 16 countries.

*For more information, see MSF's policy brief "Making the Switch: Saving More Lives with Optimal Treatment for Drug-Resistant Tuberculosis"<sup>22</sup>*

<sup>c</sup> Lzd dose in BPAL is 1,200mg per day, while the standard dose used today is 600mg per day.

## 2. A MORE AFFORDABLE PRICE FOR BEDAQUILINE

Since 2014, a coalition of groups including MSF has been engaging with the pharmaceutical corporation Johnson & Johnson (J&J) regarding the high price of bedaquiline, demanding that J&J lower the price of this breakthrough drug to no more than a US\$1 a day.<sup>23</sup> Bedaquiline should be affordable and accessible for those who need it, in order to benefit as many people with MDR-TB as possible.

Six years after initially offering bedaquiline at tiered pricing rates of US\$900, US\$3,000 and US\$30,000 for low-, middle- and high-income countries, respectively, J&J currently sells bedaquiline for US\$400 per 6-month treatment course (US\$67/month) to countries eligible to buy the drug through the GDF at Stop TB Partnership,<sup>24</sup> which represent 138 countries, including several middle-income ones. As of August 2019, only 36,353 people had received bedaquiline worldwide since it was approved for use in 2012.<sup>d</sup> At this price, MSF's target regimen price of US\$500 is not yet a reality. Bedaquiline-containing regimens of 6-18 months for MDR-TB treatment range from US\$1,000 to US\$2,000, with bedaquiline as the main driver of the high price. Many people with MDR-TB will need more than 6 months of bedaquiline and in some cases, up to 20 months, which drives the price higher. At US\$1 per day for bedaquiline, the price of bedaquiline would be US\$600 per person. This lower price is especially important for patients with resistance patterns who require both the longer course of bedaquiline and the addition of delamanid; such regimens are priced up to US\$8,000 per person. Researchers have calculated that bedaquiline could be produced and sold at a profit for much less — as little as 25 cents per day if at least 108,000 treatment courses are sold per year.<sup>25</sup>

J&J has a clear responsibility to do more to ensure affordable access to bedaquiline, as does any pharmaceutical corporation that receives public funding and support from the larger medical and public health community to bring drugs to market. Bedaquiline was the first DR-TB drug to be developed in over half a century, and its development benefitted from considerable public investment, subsidies and tax credits, reflecting a substantial portion of the estimated costs of its development.<sup>26,27</sup> Evidence that informed the use of bedaquiline, including its potential to improve cure rates with fewer side effects, was not generated by J&J and its partners alone, but also by global TB researchers and treatment providers. Substantial public investments and contributions to building the evidence base for the therapeutic value of bedaquiline came from the US government through the National Institutes of Health (NIAID) and USAID; UNITAID; health ministries in countries with high rates of TB; the South African Medical Research Council; academic institutions (University of Cape Town, University College London); non-governmental organisations (including MSF); and a host of philanthropic donors.



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Gracy Chingnuamkin lives in Churachandpur, India and is shown here receiving home-based DR-TB care from MSF. In this home visit, a nurse from MSF discusses with Gracy the importance of taking all of her pills.

Moreover, as bedaquiline was also granted orphan drug designation in the US, J&J further benefitted from a 50% tax credit on qualifying clinical R&D expenditure, as well as exclusive US marketing rights for seven years. In addition, J&J received a Priority Review Voucher (PRV) from the US FDA for registering a drug for a tropical disease. PRVs can be used to expedite FDA review of another product, or sold; PRVs have been sold for US\$67-350 million. J&J used its PRV to expedite FDA review of guselkumab (Tremfya), a blockbuster psoriasis drug, getting a four-month jump on the market. This drug sells for nearly US\$60,000 per patient per year in the US and is predicted to yield nearly US\$3.5 billion in sales for J&J by 2024.<sup>26</sup>

It is therefore unacceptable that J&J alone sets the price, effectively deciding who can have access to bedaquiline. The medicine can only reach the people who need it if J&J prices it affordably and registers it widely—and stops standing in the way of other manufacturers that want to make more affordable generic versions available.

<sup>d</sup> DR-TB STAT, e-mail communication, 2019 Sep 16.

### 3. PRO-ACCESS PRICING, LICENSING AND PATENT POLICIES

#### What We Currently Face

##### High drug prices

The key patented DR-TB medicines, **bedaquiline** and **delamanid**, are still priced too high by their respective originator companies, J&J and Otsuka (Table 2).

Delamanid is one of the most expensive DR-TB drugs and contributes significantly to the costs of treating people with MDR-TB and XDR-TB. Delamanid is priced at US\$1,700<sup>28</sup> for

6-month treatment through the GDF. Mylan, which licenses the drug from the patent-holder Otsuka, will charge an estimated US\$940 for a 6-month treatment course (US\$157 per month) as of 1 June 2020 to the government of South Africa.

**Imipenem-cilastatin** remains a niche compound with low demand for both TB and other infectious diseases, maintaining a price that is still too high to allow broader access for the most complex cases of DR-TB.

**TABLE 2: HIGH PRICES OF KEY DR-TB MEDICINES**

Medicine	Current price per patient per month	Target price per month for generic versions*
Bedaquiline	Countries purchasing through GDF <sup>24</sup> + South Africa: <sup>29</sup> Janssen (J&J) US\$67 CIS and Georgia: Pharmstandard US\$246	US\$8-17
Delamanid	Otsuka US\$283	US\$5-16
Imipenem-cilastatin	Lowest GDF price (multisource) US\$366	N/A

\*Target price ranges are based on the estimated costs of active and inactive pharmaceutical ingredients, formulation, packaging, and a cost-plus model, which includes a reasonable profit margin. Prices could reach these levels with adequate market competition and transparency.<sup>25</sup>

GDF, Global Drug Facility; CIS, Commonwealth of Independent States

**TABLE 3: REDUCED PRICES OF DR-TB MEDICINES**

Medicine	Current price per patient per month*	Target price per month for generic versions**	% change in GDF price for single drug, 2015 to 2019
Linezolid (600mg)	US\$13	US\$5-13	-1,110%
Moxifloxacin (400mg)	US\$10	US\$4-8	-159%
Clofazimine (100mg)	US\$15	US\$4-11	-119%
Prothionamide (250mg)	US\$5	US\$3-7	-49%
Levofloxacin (500mg)	US\$2.50	US\$7-17	-47%

\*Lowest GDF price (multisource)

\*\* Target price ranges are based on the estimated costs of active and inactive pharmaceutical ingredients, formulation, packaging, and a cost-plus model, which includes a reasonable profit margin. Prices could reach these levels with adequate market competition and transparency.<sup>25</sup>

GDF, Global Drug Facility

#### LOWER DRUG PRICES FOR OLDER AND REPURPOSED DRUGS

Prices for **linezolid**, **moxifloxacin**, **prothionamide** and **levofloxacin** (500mg) have decreased considerably, compared to previous years (Table 3). This is due to GDF's market-shaping role through its pooled procurement mechanism supplying more than 130 countries, which enhances competition across manufacturers of quality-assured generic medicines. These lower prices are expected to allow savings in national TB programme budgets, since linezolid, moxifloxacin and levofloxacin are Group A medicines strongly recommended for inclusion in all regimens (unless contraindicated) in the 2019 WHO guidelines.

**Clofazimine** is a Group B medicine recommended as an agent of second choice. At the end of 2018, two generic manufacturers, Macleods and Dong A, brought new quality-assured versions of clofazimine to the market, bringing much-needed competition to Novartis's monopoly.

For these five medicines, the price per patient per month is now the same or close to the generic target price this year, which many thought impossible to reach considering the relatively small size of the DR-TB market.

## Patent evergreening

Pharmaceutical corporations often rely on patenting different forms of drugs to create or extend the monopoly period, a practice known as “evergreening”. Such patent evergreening tactics, which have been used for DR-TB medicines, allow pharmaceutical corporations to maintain higher drug prices on the market while blocking the entry of lower-priced generic versions of the drugs.

**Bedaquiline:** J&J has filed for multiple patents on bedaquiline, extending beyond basic compound patents to secondary patents, staking claims on routine improvements and formulations. J&J’s patent on the primary compound is set to expire in July 2023,<sup>30</sup> and a number of TB manufacturers from India are expected to file for WHO prequalification of their generic version in anticipation of the patent expiry. In addition to the patent on the base compound, J&J has also applied for secondary patents on the use of bedaquiline to treat MDR-TB<sup>31</sup> and latent TB,<sup>32</sup> as well as the fumarate salt form of bedaquiline,<sup>33</sup> which could potentially extend the company’s monopoly until 2027 in countries where the patent is granted.<sup>34</sup>

**Delamanid:** Otsuka has filed for multiple patents for delamanid,<sup>35</sup> covering the basic compound;<sup>36</sup> active pharmaceutical ingredient (API) process and intermediates;<sup>37</sup> and formulations combining delamanid with other TB drugs.<sup>38</sup> If granted, these patents will expire between 2023 and 2031. The basic compound patent, expiring October 2023, is the most important and could block generic production (while the other patents can be circumvented by generic producers). A number of TB drug manufacturers in India are awaiting WHO guidance to see if delamanid becomes a core drug (Group A) to treat DR-TB or remains limited, which influences the demand from TB programmes, before filing for WHO prequalification of their generic version in anticipation of patent expiry.

**Pretomanid:** The compound patent on pretomanid expired in 2016 in the few high-income countries where it was filed,<sup>39</sup> and the patent was not filed in developing countries. TB Alliance’s agreement on the global exclusive rights to this compound ensures that pretomanid would be made available royalty-free in endemic countries.<sup>40</sup> However, as discussed below, TB Alliance’s licensing practices are problematic.

## Limited and non-transparent licensing

Non-exclusive licensing and transparency of licensing conditions are critical to ensuring access to essential DR-TB medicines. Transparency of drug-license terms and conditions (e.g., coverage of countries with high DR-TB burden, coverage of adult and paediatric formulations, restrictions on sourcing of the API for manufacturing finished formulations) help determine if the licensing agreement is in line with public health needs, or is just a mechanism to ensure monopoly control of the market.

**Bedaquiline:** J&J refused to license bedaquiline to the Medicines Patent Pool (MPP), which would allow sublicensing to generic manufacturers and facilitate alternative sources of quality versions of the drug for DR-TB programmes in low- and middle-income countries. J&J’s commercial agreement with Pharmstandard in 2012 has not been made publicly available and has not resulted in a reduction of prices in Commonwealth of Independent States (CIS) countries, several of which are high-burden DR-TB countries, and Georgia (Table 2).

**Delamanid:** Instead of licensing the adult formulation of delamanid to MPP, Otsuka entered an agreement, yet to be made public, in 2017 with Mylan<sup>41</sup> regarding the drug’s distribution in India, South Africa, and where Otsuka has no commercial presence. A similar license was signed in 2017 by Otsuka with R-Pharm,<sup>42</sup> the terms and conditions of which were also not made public.

According to Mylan, it plans to market delamanid tablets from its Indian facilities by mid-2020, using API sourced from Otsuka with a lower cost of production compared to Otsuka’s production in Japan. Once Mylan is also able to produce the drug using its own API, the price can decrease even further. Mylan has offered the South African government a 6-month course of delamanid for US\$940 (US\$157 per month) as of mid-2020. While this is lower than the current US\$1,700 for 6-month treatment, the price should be much lower and offered to all countries. Uncertainties remain regarding the pricing strategy of R-Pharm for delamanid in its commercial area once local registrations are granted.

In 2017, Otsuka signed a Memorandum of Understanding (MoU) with MPP to accelerate the development and manufacturing of, and access to, paediatric formulations containing delamanid for DR-TB.<sup>43</sup> However, not a single manufacturer has come forward to develop these paediatric formulations. As current volumes for both the adult and paediatric formulations of delamanid is limited, generic drug manufacturers may be waiting for patent expiry in 2023 to enter the market with adult formulations before developing paediatric formulations, given that the small market for paediatric treatment is not deemed economically viable.

**Pretomanid:** TB Alliance granted its first license to Mylan to manufacture, register and commercialise pretomanid, for the BPaL (bedaquiline + pretomanid + linezolid) regimen, exclusively in 75 upper-middle- and high-income countries, and until November 2020 in 140 low- and middle-income countries. Despite being a non-profit organisation and receiving taxpayer and philanthropic support for the development of pretomanid, TB Alliance has declined to provide a non-exclusive license to the MPP, which could allow for generic competition, and has refused to make its agreement and license with Mylan publicly available, despite requests from civil society.<sup>44</sup>

## What We Urgently Need

Patenting and licensing barriers to bedaquiline and delamanid must be overcome to increase DR-TB treatment access. For bedaquiline, J&J and Pharmstandard, and for delamanid, Otsuka and Mylan need to reduce the prices of these drugs to allow more patients to be treated. As a major supplier of generic TB medicines, generic producers, including in India, need to be encouraged to develop finished formulations of both drugs and begin preparations for WHO prequalification and regulatory approval in high-burden DR-TB countries, in anticipation of these drugs’ patent expiries in 2023 (see Annex 4).

In this context, knowledge and correct application of a legal safeguard known as the “Bolar exemption” is critical. This allows generic manufacturers to make and use a patented DR-TB drug for purposes related to regulatory approval and quality assurance, before the term of the patent expires. A High Court in India recently reaffirmed that India’s Bolar exemption under the country’s patent laws allows for export of patented medicines for experimental and regulatory purposes.<sup>45</sup> The use of the Bolar exemption should be encouraged.

Also, for bedaquiline, patent challenges need to be scaled up in high-burden DR-TB countries in which the secondary patent applications on the fumarate salt form of the drug are still pending. As India is a key manufacturing country, the patent application on the fumarate salt has been challenged in India first by networks of people living with HIV and in 2019 by DR-TB survivors.<sup>46</sup> In countries where the fumarate salt patent is granted, the threat of strict patent enforcement by J&J may delay the entry of affordable generic versions until the end of 2027.<sup>33</sup> In such countries, health ministries could consider using health safeguards such as compulsory licensing to open up supply from alternative manufacturers, as advocated for by Indian civil society.<sup>47</sup>

## 4. GOVERNMENTS ADOPTING PRO-ACCESS REGISTRATION AND PROCUREMENT POLICIES

The Global Fund to Fight AIDS, Tuberculosis and Malaria has helped to scale up access to affordable, quality-assured medicines and diagnostics that have saved millions of lives. However, following stagnating donor funding globally,<sup>48</sup> the Global Fund has in recent years revised its policies that determine funding for countries, including its funding allocation methodology,<sup>49</sup> and its Sustainability, Transition and Co-financing (STC) policy.<sup>50</sup> As a result, countries that are co-financing or transitioning from the Global Fund are more rapidly shifting from Global Fund-supported procurement mechanisms, to national processes for the purchase of medicines and diagnostics for the three diseases.

The Global Fund's revised STC policy requires all countries, even those with the lowest incomes, to gradually increase their co-financing of disease programmes, including through purchasing medicines and diagnostics. This shift risks the loss of a number of the benefits associated with Global Fund's support and pooled procurement mechanism, namely lower prices, quality assurance, and stable supply, unless the right policies and practices are put in place.

In addition to addressing these specific risks, for its part to promote sustainability of national programmes and mitigate risks inherent in the process of co-financing and transition, **the Global Fund should:**

- **Assess** and act upon risk and readiness assessments for countries in transition or co-financing, and exempt countries from co-financing commitments for the purchasing of medicines and diagnostics if issues are identified
- **Provide flexibility and safeguards** in co-financing agreements and facilitate access to its Pooled Procurement Mechanism (PPM)<sup>e</sup> and emergency procurement mechanism, as well as Stop TB Partnership's GDF

### MSF AND THE GLOBAL FUND PROCUREMENT CLIFF

MSF has witnessed problems linked to the accelerated shift to national purchasing processes following changes in Global Fund policies and funding decisions.<sup>51</sup> In Armenia, a national tender for first-line TB medicines failed because no company responded, resulting in a drug stock-out; this occurred despite this risk of failed tenders being identified in Armenia's Global Fund transition readiness assessment. In Guinea, where financial and health systems are still recovering from the 2014-2016 Ebola epidemic, the supply of HIV drugs was interrupted largely due to Global Fund co-financing expectations that exceeded the capacity of national purchasing systems. The Stop TB Partnership's GDF has also documented a number of problems.<sup>52</sup>

### Risk #1: Affordability

The benefits of Global Fund-supported purchasing processes have been achieved largely through the Global Fund PPM<sup>53</sup> for HIV and malaria, and through the Stop TB Partnership's GDF for TB.<sup>54</sup> These pooled orders result in higher volumes by aggregating demand, which attracts multiple suppliers offering competitive prices. By contrast, purchasing medical products using national processes for smaller volumes reduces competition among suppliers and leaves countries with substantially less negotiating power – leaving them vulnerable to paying higher prices.

**To ensure affordability, governments should:**

- Revise purchasing requirements to allow the use of international pooled mechanisms (such as the PPM or GDF) for certain lifesaving products
- Ensure transparency throughout the purchasing and tendering process, including by publishing final agreed prices and other commitments as outlined in the World Health Assembly resolution on drug-price transparency<sup>55</sup>
- Utilise TRIPS flexibilities and other safeguards to encourage additional suppliers, increase competition, lower prices and better ensure sustainable supply
- Remove value-added tax (VAT) and any other taxes, tariffs and distribution mark-ups on medicines and diagnostics

### Risk #2: Quality

Another negative consequence of these policy shifts relates to the quality of medicines. Medicines purchased with Global Fund support must comply with the organisation's stringent Quality Assurance (QA) Policy,<sup>56</sup> which ensures that medicines and diagnostics meet recognised standards for quality, safety and efficacy. The QA policy requires medicines to be prequalified by the WHO Prequalification (PQ) Programme or authorised for use by a stringent drug regulatory authority (SRA). Since most national purchasing processes do not require WHO PQ or SRA approval, and some regulatory authorities may not have the capacity to fully assess the quality and safety of medicines, national purchasing processes introduce the risk of purchasing products of unknown quality.

**To ensure quality, governments should:**

- Include quality-assurance requirements such as WHO PQ/SRA approval in national tenders

### Risk #3: Supply

In the context of diminishing donor support for national TB programmes, local drug registration becomes even more crucial to ensure sustainable supply of TB medicines, as it is required in most government tenders to purchase medicines. Unregistered medicines can also be blocked at customs during importation procedures. Today, not all the key DR-TB medicines are registered in all high-burden TB countries. Bedaquiline is registered in 14 out of the 30 high-burden DR-TB countries.<sup>57</sup> Delamanid is registered in only 7 high-burden DR-TB countries. For pretomanid, the TB Alliance and Mylan are urged to ensure timely submissions for registration in DR-TB endemic countries.

<sup>e</sup> The PPM (for HIV and malaria products procured via the Global Fund online platform Wambo.org) should ensure access to and transparency of Global Fund-negotiated prices for countries procuring with domestic funds and/or transitioning from Global Fund support. Global Fund should also work to address the challenges for those countries unable to utilise PPM/Wambo, or facing other financial or regulatory barriers to effective procurement.

To support manufacturers and countries in TB drug registration, the WHO Collaborative Registration Procedure (CRP)<sup>58</sup> has increasingly promoted a 90-day registration process for WHO PQ or SRA-registered medicines. As of August 2019, 41 countries had joined the WHO CRP for WHO PQ medicines, and 22 for SRA-registered ones. Not all high TB burden countries are making use of this mechanism, though all of them would benefit from it. Through August 2019, the WHO CRP was used 107 times to locally register a TB medicine.

A benefit of Global Fund-supported purchasing processes is that it circumvents the problem of corporations failing to register products in countries that are considered unattractive markets. Unfortunately, not all governments issue import waivers in

a timely manner for unregistered but needed medicines and diagnostics, thereby creating delays in supply.

*To ensure supply, governments should:*

- Join the WHO CRP<sup>58</sup> to facilitate national registration of medicines
- Enable expedited registration of WHO PQ or SRA-approved medicines
- Use import waivers (for example, for humanitarian, public health emergency or public non-commercial use), while national registrations for certain lifesaving products are pending

*For more information, see MSF's policy brief "Beware the Global Fund Procurement Cliff".<sup>51</sup>*

## 5. GOVERNMENTS SUPPORTING PUBLIC HEALTH-DRIVEN R&D AND BETTER GOVERNANCE OF MEDICINES

### What We Currently Face: Regressive Policies and 'Business As Usual'

The UK's Review on Antimicrobial Resistance estimated that "of the 10 million total deaths that might be associated with drug resistance each year by 2050, around a quarter will come from drug-resistant strains of TB."<sup>59</sup> For too long, TB and DR-TB – like other diseases that are not seen as profitable for a market-driven system – have experienced failures in the R&D system.

Our current R&D ecosystem is built on flawed incentives and premises. The development of new drugs usually results from a collective effort, with multiple public and private partners contributing to the different phases of the R&D process, and financing coming from multiple public, private and philanthropic sources. Yet, at the end of the R&D process, one stakeholder generally has exclusive control of the product, typically a pharmaceutical company. Through patents and other exclusive rights, in particular marketing-authorisation rights, this stakeholder controls supply, pricing, registration and availability, and de facto determines who has access – and who does not.

This ecosystem fails in many different areas, from a lack of new antibiotics development to unaffordable hepatitis C drugs. The current market-driven model—in which the company's goal is to maximise the financial return on developing and selling medical products—is made possible by providing companies monopoly rights to charge exorbitant prices with minimal transparency. This leads to price gouging and threatens even the wealthiest health systems.

In half a century, only two new drugs have been developed, approved and delivered to people with DR-TB: bedaquiline and delamanid. A third new drug, pretomanid, has only very recently been approved for use in combination with bedaquiline and linezolid for treating people with XDR-TB or treatment-intolerant or non-responsive MDR-TB. Much of the research to establish the clinical value of bedaquiline was done by the TB community, and financed by public and philanthropic sources, who also supported some of J&J's trials. Pretomanid was developed by the TB Alliance, a non-profit product development partnership that was established with the specific mission to develop and deliver affordable and accessible new treatments for TB, financed by public and philanthropic donors. Yet affordability, transparency and access to newer drugs remain a challenge.

Also, to properly treat TB, drugs must be used in combination. Yet the current commercial monopoly-based system favours the development of single drugs over collaboration towards regimen development, while limiting or delaying the availability of drugs to be tested as part of patient-friendly regimens. To fill this innovation gap and reduce the time to patient for newer drugs, MSF has taken the extraordinary step of running two clinical trials in order to test regimens containing combinations of bedaquiline and delamanid, and bedaquiline and pretomanid.<sup>60</sup>

In 2018, UN member states also committed "to create an environment conducive to research and development of new tools for tuberculosis, and to enable timely and effective innovation and affordable and available access to existing and new tools and delivery strategies and promote their proper use, by promoting competition and collaboration."<sup>61</sup> While a yawning funding gap of US\$1.3 billion remains,<sup>62</sup> governments committed to play their parts at the UN High-Level Meeting on TB in 2018, by mobilising US\$2 billion annually, recognising the shared responsibility of funding R&D.<sup>61</sup> As private-sector investment in TB R&D continues to decrease year on year (in 2017, 66% of funding for TB research came from the public sector while 19% came from philanthropies<sup>62</sup>), public funders and member states must find ways to close this funding gap and create the research-enabling environment to develop the new health tools that people need.

### What We Urgently Need:

In parallel with accelerating access to current treatments, we need to develop new treatment regimens with novel classes of drugs in order to give people living with DR-TB the best chance of a cure. These drugs must use unique mechanisms of action against TB bacteria, for which resistance has not already developed. But resistance will develop in time, so we need a healthy pipeline of new drug candidates to deliver continuous improvements to DR-TB treatment.

Without collaboration, innovation is compromised. Pharmaceutical corporations need to provide access to their compound libraries, and researchers need to share molecules and data, to facilitate regimen development. For example, the pharmaceutical corporations Sequella and Pfizer refused to allow access to all existing clinical data on a promising drug candidate, sutezolid.<sup>63</sup> This lack of cooperation set back development of this drug candidate by years while studies were redone by TB Alliance to replicate already existing data.

We urgently need an R&D ecosystem that rewards improving patient health outcomes and incentivises collaboration towards effective, safe and affordable new treatments, and sustainable access to them for people in need wherever they live. Such an ecosystem – one conducive to developing and delivering novel effective regimens – could comprise the following elements:

- Innovative prize funds and public-interest-focused milestone payments, such as the Life Prize,<sup>64</sup> that can result in needs-driven medical innovations without monopoly control
- Open-source collaborative research that shares data generated in preclinical research and clinical trials, and shares drug molecules to facilitate regimen development
- Public support of R&D that translates into public health impact, and clear access conditions attached to public funding in order to ensure affordability and accessibility of new health tools
- Non-exclusive licensing, including to the Medicines Patent Pool (MPP), such as through open-access schemes
- Transparent and equitable pricing in which drugs are priced at margin over cost of goods to ensure manufacturing is economically viable while enabling patients to afford the drugs they need
- Transparency on all costs incurred in the research, development, production and sales of medical products (R&D costs, costs of goods, and prices)
- A shared responsibility of all stakeholders in making health tools accessible: a responsibility for pharmaceutical corporations that receive public funding and support from the larger medical and public health community to bring drugs to patients; a responsibility of governments to ensure proper governance of medical tools and prevent monopolies from standing in the way of access; a responsibility of the research community to prioritise people's health needs and work towards affordable access to treatment for those who need it; and the translation of shared efforts into joint decision-making over access to health tools.

## NEW DR-TB TREATMENT REGIMENS: WHAT WE NEED<sup>65,66,67</sup>

- **All oral treatment** (*no injectables*)
- **Shorter duration** (*6-9 months*)
- **Effective for all forms of DR-TB** (*including RR-, MDR-, XDR-, pulmonary and extra-pulmonary TB*)
- **Effective formulations for children as well as adults**
- **Cocktail of novel classes of drugs** (*each from a distinct class of drugs, including at least 2-3 from a new drug class*)
- **Less toxic, with limited side effects** (*requiring minimal routine safety monitoring*)
- **Minimal drug-drug interactions** (*particularly with antiretroviral therapy*)
- **Easy to transport, store and administer** (*no cold chain, long half-life, simple dosing schedule*)
- **Affordable** (*less than US\$500 per treatment course*)



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Halyna Uvarenko receives counselling from an MSF nurse about her DR-TB treatment and upcoming discharge from Zhytomyr Regional TB Dispensary in Ukraine. MSF began providing treatment in 2018 in Zhytomyr region, which has one of the highest rates of TB in the country.

# CONCLUSION

In recent years, with the release of new curative medicines and patient-minded improvements of treatment guidelines, DR-TB no longer has to be a death sentence. Countries, policymakers and

health care providers tasked with reaching and treating people living with DR-TB must increase action against this persistent scourge through concrete policies and practices (Table 4).

**TABLE 4: POLICIES AND PRACTICES TO FACILITATE ACCESS AND REDUCE TIME TO PATIENT FOR NEW TREATMENTS**

<b>Target product profile (TPP)</b>	TPP is based on health needs with an affordability target built in. The specifications should include formulations for adults and children, and transport, storage and administration considerations, as well as provision for comprehensive drug-drug interaction studies
<b>Transparency</b>	<ul style="list-style-type: none"> <li>• R&amp;D costs and internal/external funding levels</li> <li>• Prices and pricing policies (across countries)</li> <li>• Licensing agreements and plans</li> <li>• Registration strategy and status</li> <li>• Patent status</li> </ul>
<b>Access to trial data</b>	Trial and preclinical trial data are shared, available upon request, or available on a common information platform
<b>Access to compounds</b>	Researchers have access to compounds and their formulation in proper quantities for testing regimens and carrying out drug-drug interaction studies
<b>Licensing</b>	<ul style="list-style-type: none"> <li>• Proprietary owners/patentees issue transparent non-exclusive voluntary licensing for all low- and middle-income countries and those with high TB burdens</li> <li>• Licensing agreement with the Medicines Patent Pool as a preferred strategy to make agreements transparently available</li> </ul>
<b>Early access/compassionate use</b>	Provision for early access and compassionate use is established with non-onerous requirements, such as pharmacovigilance
<b>WHO approval and normative guidance</b>	<p>In a timely manner:</p> <ul style="list-style-type: none"> <li>• WHO guideline committee is convened and WHO issues guidance</li> <li>• Drug is added to Essential Medicines List</li> <li>• Drug is added to Prequalification (PQ) Expression of Interest</li> <li>• Drug dossiers are submitted to WHO PQ Programme</li> <li>• Procurement entity (GDF) issues request for priority Expert Review Panel (ERP)<sup>68</sup> review of the product (ERP approval enables procurement pending full WHO PQ)</li> <li>• WHO retrains Global Laboratory Initiative (GLI)<sup>69</sup> and Green Light Committee (GLC)<sup>70</sup></li> <li>• New guidelines are disseminated through regional and country WHO mechanisms</li> </ul>
<b>Market dynamics and entry</b>	UNITAID and other global health actors support an existing agency to carry out market forecasting, analysis and entry, including encouraging generic manufacturers to ensure sustainable supply and affordable prices
<b>National regulatory frameworks</b>	<ul style="list-style-type: none"> <li>• Manufacturers submit drug for the WHO Collaborative Registration Procedure (CRP)</li> <li>• Manufacturers submit dossiers to National Drug Regulatory Agencies (NDRAs), prioritising high-burden countries, and make public the registration plan and status</li> <li>• NDRAs consult TB clinicians and TB programme on the medical need for the drug/regimen at the time when dossier is filed</li> <li>• NDRAs prioritise the dossier for evaluating novel classes of TB drugs</li> </ul>
<b>Funding rollout</b>	<ul style="list-style-type: none"> <li>• WHO develops a “transition” plan to phase out older/less optimal therapies and implement new guidance with role for Global Fund and donors</li> <li>• Countries include implementation of new guidance in concept notes and revise/re negotiate grants accordingly</li> <li>• The Global Fund TB Situation Room tracks/acts on progress/delays</li> </ul>

Governments today have the opportunity – and obligation – to make the switch to the new 2019 WHO treatment guidelines, providing improved, easier-to-take all-oral treatment regimens that no longer use toxic injectable agents and prioritise the newer drug bedaquiline. Treatment outcomes for people with MDR-TB and XDR-TB have remained unacceptably low for many reasons, including drug toxicity, long treatment durations, and limited treatment options, but the new WHO recommendations are a step in the right direction.

Immediate actions to boost access to lifesaving DR-TB drugs must be taken. MSF demands J&J/Pharmstandard and Otsuka/Mylan reduce the price respectively of bedaquiline and delamanid, so these medicines can be made available now to all who need it to survive. Patent restrictions and exclusive licensing of bedaquiline and delamanid must be countered to increase access to these newer drugs.

All high-burden DR-TB countries need to register all currently available DR-TB medicines, so that drug supplies are stable. As countries face the Global Fund “cliff” of losing funding,

technical support and access to pooling mechanisms for TB drug procurement, these countries must take measures as recommended to ensure DR-TB medicine affordability, quality and supply. The Global Fund, WHO and other stakeholders must do their parts to support these countries by providing timely assessments, technical assistance, approval processes and flexibility.

The innovation system for new health tools must change. Affordable and equitable access of health tools must be incorporated into the development process from the very start and within each funding, research and licensing agreement. R&D for new TB-care tools must be an open-source and collaborative effort, based on public-health needs rather than financial gain. Finally, shared efforts in R&D by multiple stakeholders must translate into joint decision-making over the use of and access to health tools: the monopoly rights of one company cannot prevent delivering new medicines to people who need them. Only through such broader change, coupled with immediate actions for treatment access, can we consider that we are putting up a worthy effort against DR-TB.

# ANNEX 1: SUMMARY TABLE OF DRUG PRICES PROVIDED BY PHARMACEUTICAL COMPANIES

The price corresponds to the price of one unit (tablet, capsule, etc)

Percentages indicate price evolution (in USD) of the lowest available GDF price\* comparing 2015 to 2019

Drug	GDF indicated prices (2015)	GDF indicated prices (07.2019)	All known SRA and/or PQ approved and/or Expert Review Panel temporary approved sources**												
<b>AMIKACIN</b>			Medochemie	Pharmatex	Pharmathen Hellas	Qilu Pharmaceuticals	Vianex								
500mg/2ml solution for injection	0.678 - 0.805	0.621-0.683 -9%	X	X	X	X	X								
<b>BEDAQUILINE</b>			Johnson & Johnson / Janssen Cilag												
100mg tablet	0.00 Donation	2.128	X												
<b>CLOFAZIMINE</b>			Novartis	Macleods	Dong A										
50mg soft-gel capsule	0.547-0.713	0.358 -53%	X												
100mg soft-gel capsule	1.095-1.267	0.500-0.900 -119%	X		X										
50mg tablet	-	-		X											
100mg tablet	-	-		X											
<b>CYCLOSERINE</b>			Cipla	Dong A	Macleods	Strides	Biocom JSC	Chao Centre	Mylan						
125mg cap	-	0.450			X										
250mg cap	0.187-0.330	0.240-0.263 +22%	X	X	X	X	X	X	X						
<b>DELAMANID</b>			Otsuka												
50mg film coated tab	2.530	2.530	X												
<b>ETHIONAMIDE</b>			Macleods	Cipla	Lupin	Microlabs									
125mg dispersible tablet	-	0.130	X			X									
250mg tablet	0.062 - 0.080	0.089-0.106 +30%	X	X	X	X									
<b>IMIPENEM / CILASTATIN</b>			Demo	Sunpharma	PanMedica / Panpharma	Fresenius Kabi	Labatec								
500mg / 500mg, powder for injection	-	3.050	X	X	X	X	X								
<b>LEVOFLOXACIN</b>			PT Kalbe Farma	Cipla	Hetero	Macleods	Microlabs	Denk Pharma	Medochemie	HEC Pharm	MSN Lab				
100mg dispersible tablet	-	0.129				X	X								
250mg tablet	0.033-0.055	0.027-0.030 -22%		X	X	X	X	X	X	X	X				
500mg tablet	0.059-0.097	0.040-0.047 -47%	X	X	X	X	X	X	X	X	X				
750mg tablet	0.100	0.99 -1%			X	X	X								X

Drug	GDF indicated prices (2015)	GDF indicated prices (07.2019)	All known SRA and/or PQ approved and/or Expert Review Panel temporary approved sources**							
<b>LINEZOLID</b>			Hetero	Macleods	Pfizer / Pharmacia UK	Teva	Dr Reddy's	Lupin	Cipla	Celltrion
600mg tablet	5.350-5.480	0.442-0.750 -1110%	X	X	X	X	X	X	X	X
<b>MEROPENEM</b>			Demo	PanMedica/ Panpharma	Vianex					
1g powder for injection	-	3.425	X	X	X					
<b>MOXIFLOXACIN</b>			Getz Pharma	Hetero	Macleods	Microlabs	Sunpharma	Bayer	Mylan	MSN Lab
100mg dispersible tablet	-	0.199			X	X				
400mg tablet	0.437-0.540	0.169-0.250 -159%	X	X	X	X	X	X	X	X
<b>PAS</b>			Jacobus							
4g sachet	1.333	1.333	X							
<b>PAS-SODIUM</b>			Macleods	Olainfarm						
60% w/w granules – 9.2g sachet	1.690	-	X							
Powder for oral solution – 5.52g sachet	1.370	1.320 -4%		X						
<b>PROTHIONAMIDE</b>			SW Pharma	Lupin	Microlabs	Olainfarm				
250mg tablet	0.130-0.178	0.087-0.120 -49%	X	X	X	X				
<b>TERIZIDONE</b>			SW Pharma	Macleods						
250mg capsule	1.588-1.666	1.750 +9%	X	X						
<b>NO LONGER RECOMMENDED IN 2019 WHO DR-TB GUIDELINES: kanamycin, capreomycin</b>										

\* [http://www.stoptb.org/gdf/drugsupply/drugs\\_available.asp](http://www.stoptb.org/gdf/drugsupply/drugs_available.asp) (click on Ordering List of TB Medicines)

\*\* <https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/>

GDF, Global Drug Facility; PQ, prequalification; SRA, Stringent Regulatory Authority

## ANNEX 2: DR-TB REGIMEN PRICING BASED ON NEW WHO RECOMMENDATIONS

The estimated costs of possible long and short regimens using the new WHO 2019 recommendations are presented below. All regimen prices are calculated based on Stop TB Partnership Global Drug Facility (GDF) pooled procurement prices according to the lowest price available for each quality-assured medicine in the GDF catalogue dated 13 August 2019.<sup>71</sup>

Regimen (number of months)	Regimen price based on lowest GDF price		
	2018, US\$	2019, US\$	% change in GDF price, 2018 to 2019
<b>Longer fluoroquinolone-sensitive regimens</b>			
Lfx-Bdq-Lzd-Cfz-Cs (6) / Lfx-Lzd-Cfz-Cs (12) 5 drugs in intensive phase	1,780	1,278	-28%
Lfx-Bdq-Lzd-Cfz (6) / Lfx-Lzd-Cfz (12) 4 drugs in intensive phase	1,488	915	-39%
Lfx-Bdq-Lzd-Cs (6) / Lfx-Lzd-Cs (12) 4 drugs in intensive phase	1,223	1,026	-16%
Lfx-Bdq-Lzd-Cfz (12) / Lfx-Lzd-Cfz (6)	1,888	1,315	-30%
Lfx-Bdq-Lzd-Cs (12) / Lfx-Lzd-Cs (6)	1,623	1,426	-12%
Lfx-Bdq-Lzd-Cfz (18)	2,185	1,669	-24%
Lfx-Bdq-Lzd-Cs (18)	1,911	1,786	-6%
<b>Shorter fluoroquinolone-sensitive regimens</b>			
Km-Mfx-Pto-Cfz-Z-H <sup>h</sup> -E (4) / Mfx-Cfz-Z-E (5)*	488	407	-46%
Am-Mfx-Pto-Cfz-Z-H <sup>h</sup> -E (4) / Mfx-Cfz-Z-E (5)	572	411	-28%
<b>Longer fluoroquinolone-resistant regimens</b>			
Bdq-Lzd-Dlm-Cfz (20)	8,330	7,670	-8%
Bdq-Lzd-Dlm-Cfz-Cs (20)	8,671	8,093	-6%
Bdq-Lzd-Dlm-Cfz-Cs-Imp/Cln (20)	12,316	11,680	-5%
Mfx-Bdq-Lzd-Dlm-Cfz (20) <sup>†</sup>	8,575	7,869	-8%
Mfx-Bdq-Lzd-Dlm-Cs (20) <sup>†</sup>	8,272	7,998	-3%
<b>Shorter all-oral regimens</b>			
Bdq (6)-Lzd (2)-Lfx-Cfz-Z-H <sup>h</sup> -E (4) / Lfx-Cfz-Z-E (5) <sup>‡</sup>	933	607	-35%
Bdq-Lfx-Pto-Cfz-Z-H <sup>h</sup> -E (4) / Bdq-Lfx-Cfz-Z-E (6) <sup>§</sup>	790	763	-3%
Bdq-Dlm-Lfx-Cfz-Lzd (6) <sup>§</sup>	3,313	3,122	-6%
Bdq-Dlm-Cfz-Lzd (6) <sup>§</sup>	3,297	3,108	-6%

\*Regimen no longer recommended by WHO but still used by some countries

<sup>†</sup> Mfx-based regimens should be adapted based on presence of Lfx resistance

<sup>‡</sup> Modified short regimen implemented in South Africa

<sup>§</sup> Under operational research conditions

Am=amikacin, Bdq=bedaquiline, Cfz=clofazimine, Cs=cycloserine, Dlm=delamanid, E=ethambutol, H<sup>h</sup>=high-dose isoniazid, Imp/Cln=imipenem/cilastatin, Lfx=levofloxacin, Km=kanamycin, Lzd=linezolid, Mfx=moxifloxacin, Pto=prothionamide, Z=pyrazinamide

## ANNEX 3: PAEDIATRIC FORMULATIONS TO TREAT CHILDREN WITH DR-TB

MSF supports the GDF in promoting the need for at least two suppliers for each quality-assured paediatric formulation of DR-TB medicines, in order to avoid disruptions in manufacturing and supply, and allow competition for affordability. This has been achieved for ethionamide, isoniazid, levofloxacin, moxifloxacin and pyrazinamide, but not for clofazimine (though a soft capsule from Novartis is available for older children) or cycloserine. A linezolid dispersible tablet, which only one generic company is developing, is needed, to move away from Pfizer's monopoly with their syrup formulation, the price for which is unaffordable and manufacturing irregular due to low global demand.

Products in the table below are either WHO-Prequalified (PQ) or have GDF/Global Fund Expert Review Panel (ERP) status (as of 23 July 2019).

Drug name	Company	Quality status*, †	Status period
Clofazimine 50mg tablet	Macleods	ERP	ERP status valid 1 year until June 2020
Moxifloxacin hydrochloride, equivalent to 100mg base, dispersible tablet	Macleods	WHO PQ	Since December 2018
	Micro Labs	WHO PQ	Since October 2018
Cycloserine 125mg capsule	Macleods	WHO PQ	Since July 2018
Levofloxacin 100mg dispersible tablet	Macleods	WHO PQ	Since February 2018
	Micro Labs	ERP	ERP status valid 1 year until October 2019
Ethambutol 100mg dispersible tablet	Macleods	WHO PQ	Since March 2018
Ethionamide 125mg dispersible tablet	Macleods	WHO PQ	Since May 2017
	Micro Labs	WHO PQ	Since July 2019
Pyrazinamide 150mg dispersible tablet	Macleods	WHO PQ	Since December 2016
	Micro Labs	WHO PQ	Since September 2017
Isoniazid 100mg breakable tablet	5 generic manufacturers	WHO PQ	Since 2008

\* <https://extranet.who.int/prequal/content/prequalified-lists/medicines>

† [https://www.theglobalfund.org/media/4757/psm\\_productstb\\_list\\_en.pdf](https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf)

## ANNEX 4: PATENT LANDSCAPE OF DR-TB DRUGS IN HIGH-BURDEN COUNTRIES

Drug Compound	Patent Status (as of August 2019)		
	Granted*	Pending	Not filed
<b>Bedaquiline</b> (patent application: WO2004011436)	Azerbaijan, Belarus, China, Congo (Republic of), India, Indonesia, Kazakhstan, Kenya, Kyrgyz Republic, Moldova, Mozambique, Pakistan, Philippines, Russia, South Africa, Tajikistan, Ukraine, Vietnam, Zimbabwe	Thailand	Angola, Bangladesh, Ethiopia, North Korea, Myanmar, Nigeria, Papua New Guinea, Peru, Somalia, Uzbekistan
<b>Bedaquiline fumarate salt</b> (patent application: WO2008068231)	Azerbaijan, Belarus, Indonesia, Kazakhstan, Kenya, Moldova, Mozambique, Peru, Russia, South Africa, Tajikistan, Ukraine, Zimbabwe	China, India	Angola, Bangladesh, Congo (Republic of), Ethiopia, North Korea, Kyrgyz Republic, Myanmar, Nigeria, Pakistan, Papua New Guinea, Philippines, Somalia, Thailand, Uzbekistan, Vietnam
<b>Delamanid</b> (patent application: WO2004033463)	China, India, Russia, South Africa, Ukraine	N/A	Angola, Azerbaijan, Bangladesh, Belarus, Congo (Republic of), Ethiopia, Indonesia, Kazakhstan, Kenya, North Korea, Kyrgyz Republic, Moldova, Mozambique, Myanmar, Nigeria, Pakistan, Papua New Guinea, Peru, Philippines, Somalia, Tajikistan, Thailand, Uzbekistan, Vietnam, Zimbabwe

\* Patent is set to expire in July 2023 for bedaquiline; December 2027 for bedaquiline fumarate salt; and October 2023 for delamanid. But the patent may be extended subject to patent term extensions in applicable jurisdictions. The expiry date might vary slightly depending on the how the date of filing is calculated in respective jurisdictions.

Source: medspal.org

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In Dushanbe, Tajikistan, MSF medical teams monitor the growth and development of children undergoing TB treatment. For those who are eligible, MSF supports the implementation of a shorter-course regimen that reduces the amount of time children need to be on treatment.

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