ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

# DR-TB DRUGS UNDER THE MICROSCOPE 2022

## *8TH EDITION*

## *Pricing and patent landscape of medicines for adults and children*

DOI: 10.57740/zxbm-0414

## EXECUTIVE SUMMARY

In 2021 and 2022, tuberculosis (TB) research delivered promising results about medicines and treatment regimens with the capacity to treat people affected by drug-resistant (DR)-TB more quickly and effectively, and with much-improved tolerability for patients.

As a result, BPaLM and BPaL, two new all-oral regimens, both of six months' duration, are recommended for multidrug-resistant/rifampicin-resistant (MDR/RR)-TB and pre-extensively drug-resistant (pre-XDR)-TB. These are alternatives to longer or more toxic regimens. More evidence is being generated by ongoing clinical trials assessing short all-oral regimens for fluoroquinolone (FQ)-susceptible MDR-TB and FQ-resistant MDR-TB.

Children affected by DR-TB can now be treated with regimens fully made of medicines available in child-friendly formulations. Previously, children had to be treated with adult formulations that had to be crushed or split, which carried the risk of not achieving correct therapeutic levels.

While the availability of patient-friendly medicines and regimens is a positive development, they continue to remain inaccessible to many people, in part due to their high prices and licensing arrangements by pharmaceutical corporations and other drug developers.

**Bedaquiline,** a component of all short and most long regimens to treat DR-TB in adults, currently accounts for 35-40% and 35-70% respectively of the overall cost of regimens. The compound patent on bedaquiline is set to expire in July 2023, but the restrictive terms of a voluntary license between pharmaceutical corporation Johnson & Johnson (J&J) and not-for-profit organisation TB Alliance (TBA) may act as a barrier to the entry on the market of generic versions of the drug. This will in turn delay the scale-up of more affordable bedaquiline-containing regimens.

**Pretomanid** is a component of the two new all-oral regimens recommended by World Health Organization (WHO). The medicine is currently priced at US$56/month at the Global Drug Facility (GDF). However, given the significant public and philanthropic resources that funded the development of the medicine this price is unjustified. Researchers estimate that pretomanid can be produced and sold at a profit for less than $35/month.

**Delamanid** is one of the most expensive medicines used to treat DR-TB. Its high prices – it is 13-18 times more expensive than what is estimated it could be profitably sold for – represent a major challenge to procurement of sufficient quantities of the medicine by national TB programmes and other TB care providers. Generic competition is needed to contribute to making a more affordable version of delamanid available.

Due to the impact of the COVID pandemic on health systems, the number of people diagnosed with and on treatment for TB, including DR-TB, has declined dramatically in the last two years. Now more than ever there is a need to scale up access to these shorter and more effective treatments. But to do so, pharmaceutical corporations' evergreening practices and their opaque and restrictive licensing arrangements need to be scrutinised and contested.

Given the limited number of children being diagnosed with and treated for DR-TB, manufacturers may not consider the paediatric TB market viable. It is imperative that pooling procurement across national TB programmes is considered to ensure sustainable supply, alongside stepping up efforts to diagnose and treat more children with DR-TB.

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Vaishnavi, 7 years old and living with DR-TB, held by her mother Vishaka, interacts with MSF nurse Prachi.

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## INTRODUCTION

TB was the leading cause of death from a single infectious agent until the COVID pandemic. The number of people newly diagnosed with TB in 2020 fell by 18% from the previous year due to disruptions to health systems and services caused by the pandemic, with only a partial recovery in 2021. As a result, in 2021, only one in three people with DR-TB received treatment for the disease, and the number of people provided with TB preventive treatment (TPT) was slightly lower than in 2019.[1]

This Issue Brief – the eighth in this series – by Médecins Sans Frontières (MSF)'s Access Campaign examines the current landscape and trends of DR-TB drug pricing and patents, and highlights challenges and opportunities to accelerate people's access to lifesaving regimens that are shorter, all-oral and make use of the most effective medicines. It also provides a summary of access challenges to rifapentine for TPT and drug-susceptible (DS)-TB.


Polina and Andrey are enrolled in the TB-PRACTECAL clinical trial in Minsk, Belarus. Both received six-month regimens with no injections.

## RECENT WHO RECOMMENDATIONS FOR TB

### DR-TB IN ADULTS – MAY 2022

Six-month BPaLM regimen (bedaquiline + pretomanid + linezolid + moxifloxacin) may be used in place of the nine-month regimens or longer regimens for all patients aged ≥15 years with MDR/RR-TB without previous exposure to bedaquiline, pretomanid and linezolid (defined as > one month exposure); may be used without moxifloxacin (BPaL) for fluoroquinolones (FQ)-resistant DR-TB (pre-XDR TB).[2]

The WHO recommendations are based on evidence on efficacy/safety of BPaLM and BPaL from the controlled trial TB-PRACTECAL sponsored by MSF and the ZeNix/Nix-TB trials sponsored by TBA.[3-6]

Drug susceptibility testing (DST) for FQs is strongly recommended but DST should not delay start of treatment.

Nine-month all-oral bedaquiline-containing regimens are recommended over longer regimens for adults and children with MDR/RR-TB without previous exposure to second-line treatment (including bedaquiline), without FQ resistance and with no extensive pulmonary TB disease or severe extrapulmonary TB; two months of linezolid (600 mg) can be used instead of four months of ethionamide. Confirmation of FQ sensitivity by DST is required.

People with extensive forms of DR-TB or those who are not eligible for or have failed shorter treatment regimens should receive an individualised longer regimen.

### DR-TB IN CHILDREN – MARCH 2022

In children with MDR-TB/RR-TB of all ages, bedaquiline may be used as part of short all-oral bedaquiline-containing regimens or as part of longer regimens; delamanid may be used as part of longer regimens.[7] These recommendations make it possible to design all-oral regimens for children of all ages.

### DS-TB IN ADULTS – MAY 2022

The four-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin is recommended as an alternative for patients 12 years or older with newly diagnosed pulmonary TB confirmed by a WHO-recommended diagnostic test susceptible to isoniazid, rifampicin and the fluoroquinolones.[8]

Related evidence was generated by the TBTC Study 31.[9]

### DS-TB IN CHILDREN – MARCH 2022

In children and adolescents under 16 years of age with non-severe, presumed DS-TB, a four-month regimen composed of two months of combined isoniazid, rifampicin, pyrazinamide, ethambutol followed by two months of isoniazid and rifampicin (2HRZ(E)/2HR) should be used rather than the standard six-month regimen (2HRZ(E)/4HR).[10]

These recommendations were supported by evidence from the SHINE trial.[11]

## 1. TRENDS IN DRUG AND REGIMEN PRICES

This report looks at medicines and regimens recommended by WHO for TB care. Prices come from the medicines catalogue of the Stop TB Partnership's Global Drug Facility (GDF), updated in August 2022.[12] GDF is the largest global provider of quality-assured TB products to the public sector, pooling demand across more than 150 countries. As such, the lowest prices in the GDF catalogue can be considered as benchmark prices for TB medicine purchasers.

These prices are 'ex-works' and can fluctuate during the year if, for example, a long-term agreement with different suppliers comes to an end or in case of fluctuations in prices of the active ingredients, packaging and transport costs related to it.[i]

### a. DR-TB regimens for adults

The prices of the three newer medicines, particularly delamanid, are globally the main cost drivers of DR-TB regimens in adults. Their prices at GDF remain unchanged since 2020, as shown in Table 1.

However, as shown in Table 2, where there has been competition across manufacturers of quality-assured generic medicines, GDF's pooled procurement mechanism has led to significant price decreases for other WHO Group A and B DR-TB medicines since 2015 (with the exception of cycloserine whose price dropped below its estimated cost-based generic price by 2019 before rising slightly since).[ii,iii] This translates into important savings for national TB programmes, since a combination of these medicines will be included in all the WHO-recommended regimens (unless contraindicated).

With the exception of clofazimine, the monthly price of non-patented medicines for DR-TB regimens has reached their estimated cost-based generic price. For levofloxacin 500mg and cycloserine the price is currently even lower than the estimated cost-based generic price.

**TABLE 1: PRICES OF NEW MEDICINES**

| Medicine | Current price per patient per month, US$* | Estimated cost-based generic price (per month), US$+ | % change in GDF price, 2020 to 2022 |
|---|---|---|---|
| Bedaquiline 100mg tablet | 45 | 8-17 | 0% |
| Delamanid 50mg film coated tablet | 283 | 5-16 | 0% |
| Pretomanid 200mg tablet | 56 | 11-35 | 0% |

**TABLE 2: KEY DR-TB MEDICINE PRICES REACHING ESTIMATED COST-BASED GENERIC TARGETS**

| Medicine | Current price per patient per month, US$* | Estimated cost-based generic price (per month), US$ + | % change in GDF price, 2020 to 2022 | % change in GDF price, 2015 to 2022 |
|---|---|---|---|---|
| linezolid (600mg) | 5 | 5-13 | -180% | -3,050% |
| levofloxacin (500mg) | 3 | 7-17 | +17% | -23% |
| moxifloxacin (400mg) | 9 | 4-8 | -13% | -181% |
| cycloserine (250mg) | 22.50 | 23-36 | +4% | +25% |
| clofazimine (100mg) | 15 | 4-11 | 0% | -119% |

* Lowest GDF price (multi-generic source drug)[12]

\+ 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.[13]

GDF: Global Drug Facility

i These prices take into account only the manufacturing and packaging of medicines with no additional cost linked to transport (e.g., freight, insurance, VAT, etc). Ex-works price can be referred to as ex-factory price (https://www.incotermsexplained.com/the-incoterms-rules/the-eleven-rules-in-brief/ex-works/).

ii Group A = levofloxacin or moxifloxacin, bedaquiline and linezolid; Group B = clofazimine, and cycloserine or terizidone

iii Cost-based generic prices, also referred to as target generic prices, are based on an estimation formula developed by reviewing published analyses of cost of production for medicines and assuming manufacture in India, which include costs of formulation, packaging, taxation and a 10% profit margin. These prices were estimated by researchers and first published in 2017. (https://academic.oup.com/jac/article/72/4/1243/2884272)

## TABLE 3: COST OF DR-TB REGIMENS FOR ADULTS

| Regimen (number of months) | Regimen cost based on lowest GDF prices for people of 35-50kg<br>2022, US$ |
|---|---|
| Short WHO-recommended all-oral regimens (fluoroquinolone-susceptible) | |
| Bdq-Pa-Lzd-Mfx (6)+<br>Referred to as BPaLM in 2022 WHO rapid update | 682 |
| Bdq (6)-Lfx-Cfz-Z-H[h]-E-Eto (4)/ Lfx-Cfz-Z-E (5)<br>Referred to as 9 month bedaquiline-containing regimen in 2022 WHO rapid update | 470 |
| Bdq (6)-Lfx-Cfz-Z-H[h]-E-Eto (4)/ Lfx-Cfz-Z-E (5)†<br>Referred to as 9 month bedaquiline-containing regimen in 2022 WHO rapid update | 469 |
| Short WHO-recommended all-oral regimens (fluoroquinolone-resistant) | |
| Bdq-Pa-Lzd (6)<br>Referred to as BPaL in 2022 WHO rapid update with Lzd 600 mg for as long as possible | 637 |
| Other short all-oral regimens* (fluoroquinolone-susceptible) | |
| Bdq-Lfx-Lzd-Cfz-Cs (9) | 758 |
| Bdq-Lfx-Lzd-Cfz-Z (4)/ Bdq-Lfx-Lzd-Cfz-Z (5)° | 573 |
| Dlm-Lfx-Lzd-Cfz-Z (4)/ Dlm-Lfx-Lzd-Cfz-Z (5)£ | 2,746 |
| Bdq-Dlm-Lfx-Lzd-Cfz (6) | 2,096 |
| Bdq-Dlm-Lzd-Cfz (6) § | 2,080 |
| Other short all-oral regimens* (fluoroquinolone-resistant) | |
| Bdq-Pa-Lzd-Cfz (6) ‖ | 716 |
| Bdq-Dlm-Lzd-Cfz (9) ¶ | 3,095 |
| Long WHO-recommended all-oral regimens (fluoroquinolone-susceptible) | |
| Lfx-Bdq-Lzd-Cfz (6)/ Lfx-Bdq-Cfz (12) | 1,018 |
| Lfx-Bdq-Lzd-Cs (6)/ Lfx-Bdq-Cs (12) | 1,144 |
| Lfx-Bdq-Lzd-Cfz (6)/ Lfx-Lzd-Cfz (12) | 658 |
| Lfx-Bdq-Lzd-Cs (6)/ Lfx-Lzd-Cs (12) | 784 |
| Long WHO-recommended regimens (fluoroquinolone-resistant) | |
| Bdq-Lzd-Dlm-Cfz-Cs (20) | 7,221 |
| Bdq-Lzd-Dlm-Cfz-Cs (6)/ Bdq-Lzd-Cfz-Cs (12) | 3,076 |
| Bdq-Lzd-Dlm-Cfz-Imp/Cln (6)/ Bdq-Lzd-Dlm-Cfz (12) | 7,339 |
| Dlm-Lzd-Cs-PAS-Imp/Cln (20) | 11,553 |

* Regimens currently tested in clinical trials and not yet recommended under programmatic conditions but could be used under operational research conditions

\+ Bdq: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks / Pa: 200mg once daily for 24 weeks / Mfx: 400 mg once daily for 24 weeks / Lzd: 600mg daily for 16 weeks then 300mg daily for the remaining 8 weeks (BPaLM / TB-PRACTECAL trial)

† Formerly referred to as "modified short regimen implemented in South Africa for routine use"

° Bdq: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 34 weeks / Lfx: 1000mg once daily for 36 weeks / Cfz: 100 mg once daily for 36 weeks / Z: 1500mg once daily for 36 weeks / Lzd: 600mg once daily for 16 weeks then 300mg daily for the remaining 20 weeks (endTB trial)

£ Dlm: 100mg twice daily for 36 weeks / Lfx: 1000mg once daily for 24 weeks / Cfz: 100 mg once daily for 24 weeks/ Z: 1500mg once daily for 36 weeks / Lzd: 600mg once daily for 16 weeks then 300mg daily for the remaining 20 weeks (endTB trial)

§ Bdq: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks / Dlm: 100mg twice daily for 24 weeks / Cfz: 100 mg once daily for 24 weeks / Lzd: 600mg once daily for 16 weeks then 300mg daily for the remaining 8 weeks (endTB-Q trial)

‖ Bdq: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks / Pa: 200mg once daily for 24 weeks / Lzd: 600mg once daily for 16 weeks then 300mg daily for the remaining 8 weeks / Cfz: 100 mg once daily for 24 weeks (BPaLC / TB-PRACTECAL trial)

¶ Bdq: 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 34 weeks / Dlm: 100mg twice daily for 34 weeks / Cfz: 100 mg once daily for 34 weeks / Lzd: 600mg once daily for 16 weeks then 300mg daily for the remaining 18 weeks (endTB-Q trial)

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; Hh: high-dose isoniazid; Imp/Cln: imipenem/cilastatin; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; Pa: pretomanid; PAS: P-aminosalicylic sodium; Z: pyrazinamide

## Findings

- The considerable price drop of linezolid since 2015 continues in the recent GDF tender, and has contributed to driving down the estimated costs of DR-TB regimens in line with the current WHO 2022 recommendations, as presented in Table 3.
- Similarly to 2020, only two short all-oral bedaquiline-containing regimens fall below the target ceiling of $500 called for by MSF.[14]
- BPaLM and BPaL, the two novel six-month all-oral short regimens including pretomanid recommended by WHO in May 2022, cost around $650-700.[15] The prices of these regimens will reach the target ceiling of $500 once prices of pretomanid and bedaquiline correspond to their estimated cost-based generic prices as referred to in Table 1.
- The lowest worldwide cost is still $700-1,200 per patient for long MDR-TB regimens for FQ-susceptible TB requiring 6-18 months of bedaquiline, which accounts for 35-70% of the overall regimen costs.
- Long regimens for FQ-resistant TB requiring combined bedaquiline and delamanid for 18-20 months cost $7,000 with the still-patented delamanid's high price accounting for more than 70% of the overall regimen costs. When delamanid and imipenem-cilastatin are combined for 20 months for cases of highly resistant tuberculosis and failures of previous treatment, the regimen cost surpasses $11,000.[iv]

Based on new WHO recommendations, most patients should benefit from short regimens while long regimens should only be used in a minority of patients who are either ineligible for or have not been cured with shorter regimens.

### b. DR-TB regimens for children

After more than 10 years of investments by various TB stakeholders, children affected by DR-TB can now be treated with regimens fully made of child-friendly formulations of medicines following the introduction of new linezolid 150mg dispersible tablets from pharmaceutical corporations Macleods and Micro Labs in April 2022. These replace the adult doses in tablet form that had to be crushed or split to achieve proper therapeutic levels. These formulations can all be procured through the GDF.

Pooled procurement is necessary to overcome the limited demand from various purchasers and countries in order to support manufacturers in scheduling production cycles, such as through the GDF. TB programmes need to be sensitised and encouraged to pool their procurement of paediatric formulations to ensure sustainable supply as manufacturers are often reluctant to produce an entire batch of these formulations for each TB programme tender.

With the exception of bedaquiline 20mg, delamanid 25mg, ethambutol 50mg, cycloserine 125mg and clofazimine 50mg, all the other quality-assured child-friendly formulations are marketed by two suppliers, which helps ensure their sustainable supply (Table 4).[v]

**TABLE 4: QUALITY-ASSURED CHILD-FRIENDLY DR-TB DRUG FORMULATIONS**

| Medicine | Formulation | Manufacturer(s) | Quality Assurance Status |
|---|---|---|---|
| pyrazinamide | 150mg dispersible tablet | Macleods<br>Micro Labs | PQ granted Dec 2016<br>PQ granted Sep 2017 |
| ethionamide | 125mg dispersible tablet | Macleods<br>Micro Labs | PQ granted May 2017<br>PQ granted Jul 2019 |
| levofloxacin | 100mg dispersible tablet | Macleods<br>Micro Labs | PQ granted Feb 2018<br>PQ granted Oct 2019 |
| ethambutol | 50mg dispersible tablet | Micro Labs | PQ granted Oct 2021 |
| | 100mg dispersible tablet | Macleods<br>Micro Labs | PQ granted Mar 2018<br>PQ granted Oct 2021 |
| cycloserine | 125mg capsule[vi] | Macleods | PQ granted July 2018 |
| moxifloxacin | 100mg dispersible tablet | Macleods<br>Micro Labs | PQ granted Dec 2018<br>PQ granted Oct 2018 |
| isoniazid | 50mg dispersible tablet | Micro Labs | PQ granted Mar 2020 |
| | 100mg dispersible tablet | Micro Labs<br>Macleods | PQ granted Mar 2020<br>PQ granted Mar 2021 |
| clofazimine[v] | 50mg tablet[vii] | Macleods | PQ granted Sept 2020 |
| linezolid | 150mg dispersible tablet | Macleods<br>Micro Labs | GF ERP granted until March 2023<br>GF ERP granted until April 2023 |
| bedaquiline | 20mg tablet[vii] | Johnson & Johnson (Janssen) | FDA approval May 2020 |
| delamanid | 25mg dispersible tablet | Otsuka | EMA approval Sept 2021 |

EMA: European Medicines Agency; FDA: US Food and Drug Administration; GF ERP: Global Fund Expert Review Panel; PQ: prequalification by WHO

iv Despite being a multi-source generic medicine, imipenem-cilastatin remains a niche compound with low demand for both TB and other infectious diseases. Its price is therefore still too high, even at GDF, to allow broader access for the most complex cases of DR-TB. It is important that R&D efforts are pursued to identify more new medicines active against MDR/RR-TB so that imipenem-cilastatin is not needed anymore to treat complex cases. The very same challenge is observed with meropenem.

v In addition to Macleods' tablets of clofazimine 50mg that can be dissolved in water, Novartis supplies soft capsules of clofazimine 50mg that are registered at Stringent Regulatory Authorities. Even though Novartis' product is indicated in children below 10 years, clofazimine is diluted in an oily excipient within the soft capsule which does not make this formulation adapted for its administration to all children (e.g., youngest children, children with difficulties swallowing).

vi Cycloserine 125mg capsules can be dissolved in water.

vii Clofazimine 50mg and bedaquiline 20mg tablets can be dissolved in water. Since they disintegrate after three minutes, they cannot be called 'dispersible tablets' which strictly comply with a maximum disintegration time of three minutes as per the specifications of WHO disintegration tests for tablets.

## DIAGNOSING TB IN CHILDREN

According to the WHO Global TB report 2021, 1.1 million children and young adolescents aged under 15 years fall ill with TB every year. However, more than 60% of all children with TB worldwide are never even diagnosed with the disease, and 96% of children who die from TB are never put on treatment, 80% of them younger than five years old.[16,95] Among the estimated 25,000 new DR-TB cases in children every year, fewer than 5% are diagnosed and receive treatment.[17]

To overcome the large case detection gap for children and to give a chance to those affected by DR-TB to be treated with the available child-friendly formulations, new treatment-decision algorithms are recommended by WHO. These involve diagnosing TB on clinical criteria alone, and will enable doctors to start TB treatment in children without confirmation from laboratory tests. While highly sensitive point-of-care diagnostic tests are being developed for children, chest X-ray is another useful tool as part of a treatment-decision algorithm as well as TB tests done on stool samples rather than on sputum samples, which can be challenging to collect.[18]


8-year-old Muhammad undergoing a sputum induction for TB diagnosis in a paediatric TB hospital in Dushanbe, Tajikistan

Table 5 provides regimen costs for children of 10kg and 20kg calculated based on the lowest price available for child-friendly formulations in the GDF Medicines Catalogue, August 2022.[19]

### TABLE 5: DR-TB REGIMEN COSTS IN CHILDREN USING EXCLUSIVELY CHILD-FRIENDLY FORMULATIONS§

| Regimen (number of months) | Regimen cost based on lowest GDF price 2022, US$ | |
|---|---|---|
| | Children of 10kg (approx. 1 year old) | Children of 20kg (approx. 5 years old) |
| Short all-oral regimens for non-severe disease (fluoroquinolone-susceptible) | | |
| Bdq (6)-Lfx-Cfz-Z-E-H$^{h}$-Eto (4)/Lfx-Cfz-Z-E (5)° | 500 | 648 |
| Bdq-Lfx-Lzd-Cfz (2)/ Bdq-Lfx-Cfz (7)* | 331 | 487 |
| Bdq-Lfx-Lzd-Dlm (2)/ Bdq-Lfx-Dlm (7)* | 1,134 | 1,736 |
| Bdq-Lfx-Lzd-Cs (2)/ Bdq-Lfx-Cs (7)* | 468 | 737 |
| Short all-oral regimens for non-severe disease (fluoroquinolone-resistant) | | |
| Bdq-Lzd-Cfz-Dlm (2)/ Bdq-Cfz-Dlm (7)* | 1,164 | 1,736 |
| Bdq-Lzd-Cfz-Cs (2)/ Bdq-Cfz-Cs (7)* | 498 | 738 |
| Long all-oral regimens for extensive disease (fluoroquinolone-susceptible) | | |
| Bdq-Lfx-Lzd-Cfz-Dlm (4)/ Bdq-Lfx-Cfz-Dlm (11) | 2,026 | 3,023 |
| Bdq-Lfx-Lzd-Cfz-Cs (4)/ Bdq-Lfx-Cfz-Cs (11) | 917 | 1,358 |
| Long all-oral regimens for extensive disease (fluoroquinolone-resistant) | | |
| Bdq-Lzd-Cfz-Cs-Dlm (4)/ Bdq-Cfz-Cs-Dlm (11) | 2,304 | 3,440 |

§ For adolescents and children matching the weight band of 35-50 kg, Table 3 for adults can be used as a reference

° WHO-recommended regimen

* In line with the March 2022 WHO operational handbook on TB - Module 5, children with non-severe disease can usually be treated for less than 18 months; these five examples of shorter regimens are based on expert opinion and have not been studied.[20] Therefore they should be implemented under operational research conditions.

## Findings

- Bedaquiline-containing regimens without delamanid cost less than $500 for nine-month treatment for children of 10kg and between $500 and $750 for those of 20kg. The cost of 15-month treatment is around $900 and less than $1,500 in these two groups, respectively. Bedaquiline makes up 30-60% of these regimens' overall costs, regardless of the age group.
- When bedaquiline and delamanid are combined, nine-month treatment for children of 10kg costs around $1,000 and more than $1,500 for those of 20kg. The cost of 15-month treatment reaches around $2,000 and $3,500 in these two groups, respectively. For all these regimens, delamanid accounts for 65-80% of the overall cost, regardless of the age group.

Bedaquiline and delamanid are still patented medicines for which the originator companies, J&J and Otsuka respectively, have a global monopoly blocking the generic competition that lowers prices.

Considering the limited number of children diagnosed and treated with DR-TB, the demand for child-friendly formulations of DR-TB medicines remains limited compared to the number of children in need. While research is ongoing to develop adapted diagnostic tools, all TB stakeholders, including national TB programmes, ministries of finance and donors, should mobilise the necessary resources to increase the number of children being diagnosed and treated for DR-TB. This will help ensure that pharmaceutical companies do not neglect the paediatric DR-TB market in the long term, and facilitate competition on prices between generic and originator companies (for bedaquiline and delamanid) after patent expiry.

Through their paediatric DR-TB initiative, GDF and the Sentinel Project[viii] identified early adopter countries that could implement the new paediatric formulations quickly, and pooled their demand.[21] Since 2019, around 80 countries have already procured child-friendly DR-TB medicines from GDF.[ix] This has allowed GDF to start negotiating price reductions, which will in turn make it easier to scale up access.

Dr. Zulfiya Dusmatova, medical doctor with MSF in Tajikistan.

## ONE STEP AT A TIME: IMPROVING TREATMENT OPTIONS FOR CHILDREN WITH DR-TB IN TAJIKISTAN

*Dr Zulfiya Dustmatova works as a medical doctor with MSF in Tajikistan, where our teams work with the Ministry of Health and Social Protection to diagnose and treat children with DR-TB.*

Although MSF had been treating adults with DR-TB in Dushanbe, Tajikistan, since 2009, we did not begin treating children until 2012. At that time, we did not have paediatric formulations of the medicines, so we had to split the tablets meant for adults, sometimes in half, sometimes in larger bits. We were concerned about the effect of giving children higher or lower doses of the medicines through this makeshift and inexact method. But we had no choice.

The children had to take around five to six medicines every day along with very painful daily injections for several months. The side effects of these medicines were often unbearable. I remember a girl, 14 years old, who hid her medicines because of her fear of the side effects. Her condition deteriorated, and eventually she died. Other children suffered from hallucinations and deafness brought on by the toxicity of the drugs. Parents often refused to enrol their children on treatment to avoid them suffering the side effects.

Our approach from the start was to embrace a comprehensive approach to treatment for children. This approach focuses on community-based care wherein children are looked after and treated at home as much as possible, and can therefore benefit from the support of their family and trained nurses working in the community. This helps children keep up with the long and challenging treatment.

In 2014, we were able to start using a few TB medicines in syrup form. This made it easier to treat younger children who often have difficulties swallowing pills, and it also meant we could achieve accurate dosing. However, not all the required medicines were available as a syrup and those that were available did not have a long shelf life and needed refrigeration. Not all patients' homes had refrigerators to keep these syrups at the right temperature. But it was still an improvement on the options we had when we first started treatment for children.

After feasibility studies had been conducted, we first prescribed bedaquiline for a child at the end of 2015, using the crushed adult tablets of the medicines. Then delamanid followed in 2016. Both these drugs meant that eventually we could stop using injections to treat children – it was a huge relief to be able to end the toxic daily injections of medicines.

The development of TB medicines in paediatric formulation in dispersible form marks the latest attempt to improve treatment for children. The advantages are that the tablets can be dissolved in a small amount of water—several medicines in a single cup if needed—and that they are tasteless compared to the often bitter syrups. There are also no storage challenges or need for refrigeration.

Today, in Tajikistan, we have about four or five medicines available in this form, and they have made treatment much easier and more child-friendly. Around half of the medication children take daily now is in dispersible form.

And for the future? While we welcome any further improvements in TB medicines for children, we must also continue to focus on meeting the challenges that lie with finding children with the disease in the first place. In our project we detected more than 50% of treated children through contact tracing. Without it, it will remain very difficult to get on top of this disease that continues to claim many young lives unnecessarily.

viii The Sentinel Project on Pediatric Drug-Resistant Tuberculosis is a global partnership that aims to develop and deploy evidence-based strategies to prevent child deaths from DR-TB. See: https://sentinel-project.org/about/

ix Oral presentation by GDF on 10 March 2022 at a UNICEF-UNFPA-WHO meeting

**TABLE 6: KEY DR-TB MEDICINE PRICES AND MANUFACTURERS**

| Medicine | Purchasing mechanism (examples) | Manufacturer | Price per person per month, US$* | Estimated cost-based generic prices (per month), US$° |
|---|---|---|---|---|
| bedaquiline 100mg tablet | GDF | Johnson & Johnson (Janssen) | 45 | 8-17 |
| | Russian Federation - government tender[22] | Pharmstandard | 275+ | |
| | South Africa - government tender[23] | Johnson & Johnson (Janssen) | 54† | |
| delamanid 50mg film coated tablet | GDF | Otsuka | 283 | 5-16 |
| | Russian Federation - government tender[24] | R-Pharm | 248+ | |
| | India - Central TB Division direct negotiation[25] | Viatris | 207 | |
| | South Africa - government tender[26] | Viatris | 207† | |
| pretomanid 200mg tablet | GDF | Viatris | 56 | 11-35 |

* Lowest GDF price[12]

\+ Price based on exchange rate between Rub/US$ on 12 July 2022. This price is subject to fluctuation due to the ongoing volatility of the Russian Ruble.

† Price based on exchange rate between ZAR/US$ on 24 August 2022. This price is subject to fluctuation due to the volatility of the South African Rand.

° 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.[13]

GDF: Global Drug Facility

## 2. BEDAQUILINE

Since 2020, bedaquiline has become a backbone in regimens recommended by WHO, and is used to treat almost every person affected by DR-TB.[27] However, reports of emerging resistance to bedaquiline threaten to undermine this progress, considering the limited alternatives available.[28,29]

### Price

Since July 2020, GDF can apply a 'buy 10, get 2 free' arrangement for bedaquiline 100mg orders that results in a price of $1.50/day for an adult treatment ($272/six months), based on purchase commitments between 125,000 and 200,000 treatments per year. However, considering the substantial public taxpayer funding that J&J received for bedaquiline's clinical development, as researchers estimated, it is time for its price to come closer to $0.50 per day.[13,30]

The deal between GDF and J&J is accessible to 139 countries (including major high-burden DR-TB countries such as China and India).[31] Other high-burden DR-TB countries such as South Africa and the Russian Federation are not among the 139 countries. In South Africa, bedaquiline is priced similarly to the price available through GDF. Since its entry in the Russian market in 2017, the price of bedaquiline supplied by J&J's partner, Pharmstandard, has not changed and remains six-fold more expensive compared to the GDF price (Table 6).

### Child-friendly formulation

Since March 2022, WHO recommends the inclusion of bedaquiline in all-oral regimens for children of all ages.[32] J&J manufactures tablets of 20mg that can be dissolved in a liquid, which are of significant added value for younger children and those with difficulty swallowing. The marketing authorisation for bedaquiline 20mg was expanded in 2020 by the US Food and Drug Administration (FDA) and in 2021 by the European Medicines Agency (EMA) to cover children and adolescents 5 to 18 years old. It can be procured through the GDF (at $120 and $200/six months respectively for children of 10 and 20kg) or directly through J&J (at a price which is not public).

However, bedaquiline 20mg represents 30-60% of regimens' overall costs for children of 10kg and 20kg. Therefore, more affordable quality-assured generic versions of these child-friendly tablets are needed to allow broader access for as many children as possible.

### Patent barriers, voluntary licenses and oppositions to secondary patents

Janssen Pharmaceutica N.V. (Janssen), a subsidiary of the US pharmaceutical corporation J&J, currently has monopoly over bedaquiline, and will continue to do so at least until July 2023, when its primary base compound patent is expected to start to expire.[33] This will prevent generic manufacturers from producing the medicine at least until 2023.

**TABLE 7: TB ALLIANCE'S VOLUNTARY LICENSES ON PRETOMANID AND BEDAQUILINE**

| | |
|---|---|
| **2009** | TBA enters into a royalty-free license TMC207 (now bedaquiline) with Tibotec (acquired by J&J) for the treatment of DS-TB. |
| **2010** | TBA starts developing regimens containing its own molecule pretomanid with bedaquiline for XDR-TB.[x] |
| **2011** | TBA starts developing regimens containing its own molecule pretomanid with bedaquiline for DS-TB and DR-TB. |
| **2019** | TBA licenses pretomanid to generic manufacturers for DS- and DR-TB but also grants a sublicense for bedaquiline to Viatris and Macleods, restricting commercialisation of bedaquiline for use in treating DS-TB only, based on its main license agreement with J&J. |
| **2023** | Basic patent on bedaquiline expires but Indian manufacturers may be restricted from marketing for DR-TB indication as per the terms of the TBA sublicense. |

However, in countries where secondary patents have been granted, such as South Africa, the market entry of generic bedaquiline will take longer.

In India and other countries, where secondary patents are pending and under challenge (as pre-grant oppositions) and generic manufacturers therefore have the freedom to operate, a number of them are getting ready to enter the market with quality-assured tablets of bedaquiline 100mg manufactured with their own active pharmaceutical ingredient (API). For instance, Macleods, a manufacturer in India, has already been granted Global Fund Expert Review Panel (GF ERP) status which validates its compliance to WHO quality standards.[34] However, the terms of a sublicense for bedaquiline between drug development not-for-profit organisation TBA and generic manufacturers may act as a barrier to their ability to actually enter the market.

In 2009, TBA entered into a license agreement with J&J for bedaquiline to treat DS-TB, and subsequently sublicensed the medicine to Indian generic manufacturers Viatris (formerly Mylan) and Macleods.[35] While the sublicense has not been made public, generic companies have indicated that under its terms bedaquiline can only be commercialised for supply for DS-TB indication, and not for DR-TB. Even though Indian manufacturers who have signed the sublicense would have been able to supply generic bedaquiline in 2023 for all medical indications, they may not be able to do so due to the terms and conditions of TBA's license agreement with J&J on bedaquiline.

Under the current WHO guidelines, pretomanid, another new TB medicine, is to be used in combination with bedaquiline/linezolid/moxifloxacin (BPaL or BPaLM regimens) for DR-TB care and, depending on an ongoing clinical trial, possibly in combination with bedaquiline/moxifloxacin/pyrazinamide (BPaMZ regimen) for DS-TB care in the future.[36] As shown in Table 7, on top of bedaquiline, TBA has licensed pretomanid to three Indian manufacturers for supply, including Viatris and Macleods, in treating MDR-TB and DS-TB in low- and middle-income countries (LMICs) except China.[37-39]

In the absence of TBA's agreement with J&J and the sublicense to Indian manufacturers, generic competition would have led to a price drop allowing scaled up access to cheaper bedaquiline-containing short and long regimens, wherein bedaquiline currently accounts for 35-40% and 35-70% of the overall cost, respectively.

There is an urgent need for the license agreement between TBA and J&J and the sublicenses between TBA and Indian manufacturers to be made public, so that governments and competition regulators may review them for their negative impact on the availability of affordable generic versions of bedaquiline for DR-TB. It should be clarified whether the terms and conditions in this thicket of agreements allow generic manufacturers to terminate or unbundle the sublicense on bedaquiline on the expiry of the basic compound patent in India. Furthermore, manufacturers who have not signed any licenses with TBA should be encouraged to develop generic bedaquiline.

In addition, a secondary patent application on bedaquiline's fumarate salt was filed in multiple high-burden countries, which could potentially extend J&J's monopoly until 2027 in countries where this patent is granted, like South Africa.[40,41]

Many drug molecules are administered as salts, and their preparation (as compared to their free base/acid forms) is common knowledge in the field of pharmaceuticals and should not be patented. These 'evergreening' patents unjustifiably prolong the market monopoly position of the originator company. Civil society organisations have started to challenge these applications. In May 2020, secondary patent applications on bedaquiline including the fumarate salt form were challenged in Brazil and Thailand on grounds including non-obviousness.[42] The patent application on the fumarate salt was rejected in Brazil.[43]

The patent application on the fumarate salt has also been challenged in India—by networks of people living with HIV in 2013 and by DR-TB survivors in 2019.[44] The latest opposition explicitly highlighted that the claims were not 'new' and sections were a copy-paste of material by the patent applicant from an earlier patent filing relating to an HIV drug, rilpivirine, which the Indian Patent Office had rejected.[xi]

In countries where fumarate salt patent claims have already been granted and are unlikely to be revoked, governments could consider using other TRIPS flexibilities such as compulsory licensing to open up supply from generic manufacturers. Without a compulsory license, generic manufacturers of bedaquiline may face the threat of an infringement suit from J&J until the end of 2027.

x WHO definition of extensive drug resistance (XDR) relevant in 2010: resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

xi The decision of the Indian Patent Office on Indian Patent Application Number 1594/DELNP/2007, dated 26 April 2013, can be accessed by entering the patent application number on https://ipindiaservices.gov.in/PublicSearch/PublicationSearch/ApplicationStatus

In addition to granted and pending patents on the fumarate salt, J&J also has several 'evergreening' patents[xii], including on the use of bedaquiline to treat MDR-TB and latent TB, paediatric formulation, and long-acting injectable formulation.[45-48]

In July 2020, 100% LIFE, a civil society organisation in Ukraine and a partner of the global campaign 'Make Medicines Affordable', filed the first patent opposition on bedaquiline in the Eastern Europe and Central Asia (EECA) region, in an effort to prevent a monopoly on the paediatric version.[49]

In India, the Delhi Network of Positive People together with Ganesh Acharya, a TB survivor, challenged the patent applications on the paediatric and long-acting formulations of bedaquiline in December 2020 and March 2021, respectively.[50]

If successful, these oppositions in high TB-burden countries will prevent J&J from claiming an exclusive monopoly right on paediatric formulations of bedaquiline. This will in turn facilitate the scale-up of DR-TB care for children through more affordable generic versions of the medicine.


Bedaquiline is the backbone of regimens recommended by WHO to treat DR-TB. While patents on bedaquiline start expiring in 2023, the restrictive terms of a voluntary license may act as a barrier to the market entry of generic versions of the drug.

## 3. DELAMANID

Since the WHO 2020 recommendations, delamanid is classified as a Group C medicine, meaning it can be used when a DR-TB regimen cannot be composed with Group A and B medicines.[51] In addition to the available evidence of its efficacy for DR-TB, the endTB trial for fluoroquinolone (FQ)-susceptible MDR-TB and the endTB-Q trial for FQ-resistant MDR-TB sponsored by MSF could provide further evidence regarding delamanid's impact on clinical outcomes (treatment success rates) once they are completed in 2023 and 2025, respectively.[52-54]

The role of delamanid in a rescue regimen after treatment failures with the newly recommended BPaL and BPaLM regimens remains uncertain, as there may be risk of cross-resistance with pretomanid, the other new compound from the same therapeutic class.[55] Similarly, the role of delamanid as a substitute for patients who cannot tolerate pretomanid (e.g., due to liver toxicity) still needs to be clarified.

### Price

With the exception of imipenem/cilastatin, used only for the most severe forms of DR-TB, delamanid remains the most expensive medicine recommended for DR-TB treatment. It accounts for more than 70% of the overall cost of longer regimens (18 to 20 months) to treat fluoroquinolone-resistant TB with bedaquiline and delamanid. This represents a major challenge for national TB programmes and other TB care providers to procure sufficient delamanid. Generic competition is needed to contribute to making a more affordable version of delamanid available. This will bring regimen prices down and incentivise its combined use with bedaquiline, which is necessary to protect bedaquiline from the emergence of resistance.

Through the GDF, delamanid 50mg tablets can be procured at $283/month ($1700/six months) from the originator company, Otsuka (Table 6).

Otsuka has two licensees: Viatris for most LMICs and R-Pharm for EECA countries. The three entities do not compete on prices as they operate in separate markets.

R-Pharm supplies delamanid tablets manufactured by Otsuka at $248/month to the Russian national TB programme. Other EECA countries purchase delamanid through GDF.

As a result of a technology transfer, Viatris manufactures delamanid 50mg tablets in India based on Otsuka's API premix.[56] This formulation has been granted GF ERP status until December 2022. It started to be supplied at $207/month to the national TB programmes of South Africa and India in 2020 and at the end of 2021, respectively.

Viatris has also developed its own delamanid API. Once granted GF ERP status by the end of 2022, delamanid 50mg manufactured fully in-house by Viatris should be made available for supply at less than $207/month.

Researchers have estimated that delamanid could be produced and sold at a profit for $16/month when the medicine reaches prescriptions to at least 108,000 patients.[13]

xii Filing numerous patent applications for the same medicine (evergreening) is a common practice in the pharmaceutical industry to try and delay the market entry of affordable generic medicines. Therefore, in addition to filing for a patent on a new therapeutic compound, pharmaceutical corporations routinely try to obtain patents on derivatives (salts, prodrugs, crystals, polymorphs); formulations (e.g. powders, tablets and capsules, injectables, syrups, dispersible tablets, etc.); dosage (route, regimen); combinations (e.g. a fixed-dose combination when different drugs are combined in the same pill); new use of an existing drug to extend the period of their monopoly over price and supply. Also see: https://msfaccess.org/evergreening-drugs-attack-access-medicines

## Child-friendly formulation

As per 2022 WHO recommendations, delamanid may be used as part of longer all-oral treatment regimens for children of all ages.[57]

In September 2021, Otsuka was granted regulatory approval by the EMA for delamanid 25mg dispersible tablets for children of more than 10kg. This child-friendly formulation facilitates easier treatment of smaller children and those with difficulty swallowing. It can be procured through the GDF (at $595 and $893/six months respectively for children of 10kg and 20kg) and remains accessible directly for free at Otsuka through compassionate use in countries where it is not yet registered.

After ongoing technology transfer from Otsuka, in 2023 Viatris should be able to market delamanid 25mg dispersible tablets manufactured fully in-house at a lower price compared to Otsuka's at GDF.

Delamanid 25mg currently accounts for 65-80% of the overall cost of combined bedaquiline and delamanid regimens for children of 10kg and 20kg. As with delamanid 50mg, quality-assured generic versions of the child-friendly formulation of delamanid are needed to bring its price down for greater accessibility to all children in need.

## Patent barriers, voluntary licenses and patent oppositions

The Japanese pharmaceutical corporation Otsuka, the originator company that first marketed delamanid, has filed for multiple patents on the known compound of delamanid in many LMICs.[58]

Patents and patent applications on delamanid cover the basic compound, API process and intermediates, formulations and delamanid combined with other TB drugs. These expire between 2023-2031, if granted.[59-61] Based on feedback from generic manufacturers in India, the compound patent on delamanid in India is the key patent blocking the entry of generic medicines; while others can be circumvented. The granted and pending process patents could have a potential impact on the final price of the generic compound as it would require the development of a non-infringing process which may have cost implications.[62,63] The granted patents that cover the basic compound have been challenged in Pakistan.[64]

With the basic patent on delamanid set to expire in October 2023, Indian generic companies have developed a generic version of the adult formulation and are interested in developing the paediatric formulation as well, but are facing a number of challenges.

**A key part of introducing quality-assured generic versions of a medicine is by conducting bioequivalence (BE) studies of the generic against the originator product, which is known as a reference product in regulatory terms. The purpose of these studies is to demonstrate equivalence of the generic with the reference product. To do so, generic companies require samples of the reference product. Generic manufacturers have tried to obtain Otsuka's delamanid for use as reference product. However, originator companies generally do not make product samples easily available to generic manufacturers who need them, which acts as a barrier to generic entry.**

A key part of introducing quality-assured generic versions of a medicine is by conducting bio-equivalence (BE) studies of the generic against the originator product, which is known as a reference product in regulatory terms. The purpose of these studies is to demonstrate equivalence of the generic with the reference product. To do so, generic companies require samples of the reference product. Generic manufacturers have tried to obtain Otsuka's delamanid for use as reference product. However, originator companies generally do not make product samples easily available to generic manufacturers who need them, which acts as a barrier to generic entry.The originator version of delamanid is only available within TB programmes, GDF and TB treatment providers such as MSF. Otsuka and Viatris have stringent supply agreements with these agencies, requiring them to report on each pill, bottle and country where it is used, thus preventing them from being a source of the reference product for generic companies for their BE studies. WHO and other agencies should raise awareness about the reference product availability problem to help facilitate the development of meaningful solutions, including perhaps the WHO Prequalification Programme considering establishing a process for obtaining samples that can be provided to generic manufacturers.

For the duration of the patent term, Otsuka did not license the adult formulation of the drug to the Medicines Patent Pool (MPP); instead, it entered into a secret deal in 2017 with Viatris for manufacturing and supply in India and South Africa, where the Japanese corporation has no commercial presence.[56] This is not an effective strategy to improve access and reduce prices as the monopoly of delamanid is retained with the exclusive and very limited bilateral license to Viatris. Instead, Otsuka should issue a non-assert declaration, i.e., a commitment to not enforce their delamanid patents, covering all LMICs to speed up the availability of generic sources.

Otsuka's decision to license the adult formulation of the medicine to Viatris and not to the MPP may have acted as a barrier to the market entry of generic paediatric formulations of delamanid. In 2017 Otsuka signed a Memorandum of Understanding (MoU) with the MPP to accelerate the development and manufacturing of paediatric formulations containing delamanid for MDR-TB.[65] However, this has not translated into a license, and to date, not a single generic company has come forward to develop paediatric formulations under this MoU. The limited scope of the MoU, which did not include

the adult formulation of delamanid, may have been the main reason for making it unattractive to generic producers. Generic manufacturers are therefore waiting for patent expiry in 2023 to enter the supply chain with adult formulations, which may be followed by paediatric formulations if they have access to the reference product for BE studies.

Furthermore, the license entered by Otsuka and Viatris is not transparent. Transparency of terms and conditions – for example, coverage of countries with high burden of DR-TB, coverage of adult and paediatric formulations and restrictions on sourcing of the API for the manufacture of finished formulations – can provide the basis for scrutiny, and can help the public, treatment providers and public health policymakers to determine whether the agreement is in line with public health needs or is merely a mechanism to manage competition for Otsuka to keep control of the market.

While the terms and the full text of the agreement are not available for analysis, Viatris and Otsuka refer to an ongoing technology transfer between the two companies for the paediatric formulation, after completion of technology transfer for the adult formulation and the API. The technology transfer package referred to above could potentially place additional limitations on Viatris as a licensee when patents start expiring. Based on MSF's past analysis of technology transfer terms under voluntary licenses, licensees could be restricted by license terms from supplying delamanid to countries not included in the territories of the agreement even if the compound patent has expired, or has not been filed and/or granted.[66,67]

## A PETITION TO INCREASE ACCESS TO BEDAQUILINE AND DELAMANID IN INDIA

In March 2021, Meera Yadav, an XDR-TB survivor, and the Mumbai Chapter of Jan Swasthya Abhiyan, a network of organisations and individuals working on public health, filed a petition before the High Court of Bombay in India to ensure continuous access to new TB drugs for people living with DR-TB and XDR-TB in India.[xiii]

The petition calls for a compulsory license under the Patents Act, 1970 for the two new TB drugs – bedaquiline and delamanid. If operationalised, the compulsory license would allow alternate producers to offer more affordable generic versions of the drug to the National TB Elimination Program (NTEP) at a far lower price.

Currently these two newer drugs are from a single source; the pharmaceutical companies or their licensees who hold the patents have the sole right to supply the NTEP, complicating procurement with lengthy negotiations and high prices. As a result, alternate suppliers are excluded from producing and making low-cost generic versions of the said drugs available and accessible.

Considering that TB and DR-TB represent a situation of national health emergency in India, there is an immediate need to procure bedaquiline and delamanid within a finite budget so that they can be made available to all patients who need it. The Patents Act, 1970 contains mechanisms to ensure accessibility and availability of essential medicines during a health emergency. Sections 92 and 100 of the Patents Act are meant to deal with such exigencies. Under the Act, the government can issue a public non-commercial compulsory license or a government use license to meet the requirements of the public regarding a patented drug.

The High Court of Bombay has taken note of the petition calling for a compulsory license for these new TB drugs and has asked the Government of India to provide a response. However, hearings of the petition have been significantly delayed due to the COVID pandemic.

xiii WHO definition of extensively drug-resistant TB (XDR-TB) relevant in 2020: TB that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

## 4. PRETOMANID

BPaL and BPaLM are the first two first regimens that WHO has recommended that use pretomanid.[68] However, this compound is still not classified in any of the groups of DR-TB medicines by WHO, and its potential role as a standalone compound in other regimens has yet to be defined. The safety and efficacy of pretomanid in treatment of children and pregnant women urgently needs to be established by its developer, TBA.

Molecular/genetic markers of pretomanid resistance need to be clarified (including potential for cross-resistance with delamanid since both compounds belong to the same therapeutic class), so as to facilitate the development of faster DST techniques, including molecular tests.[55]

The SimpliciTB trial from TBA is testing the combination of bedaquiline, pretomanid, moxifloxacin and pyrazinamide for four months for DS-TB and six months for MDR-TB with possible results in 2023.[69] The safety and efficacy of pretomanid in children and adolescents have not yet been established. A single-dose study of the pharmacokinetics and safety in children affected by DR-TB is scheduled once a reproductive safety study in male adults is completed by April 2023.[70]

### Price

The price for a six-month treatment course of pretomanid through the GDF is $336 ($56/month) (Table 6). However, researchers have estimated that generic versions of pretomanid could be produced and sold at a profit for less than $35/month when the medicine reaches prescriptions to at least 108,000 patients.[71]

### Voluntary licenses

Following an agreement with former biotechnology company Chiron in 2002, TBA gained global exclusive rights to pretomanid and related compounds for the treatment of TB.[72] Pretomanid was subsequently developed by TBA, who signed a non-exclusive license agreement with Viatris in 2019 for manufacture, supply and registration of the medicine.[35] TBA's license with Viatris covers global rights except in China, Hong Kong, Macau and Taiwan, where TBA is partnering with Shenyang Hongqi Pharmaceuticals to market pretomanid as part of BPaL.[73] Viatris was granted WHO prequalification status for its pretomanid 200mg tablets in 2020.[74]

Since 2019, TBA has signed two more non-exclusive license agreements with Indian generic companies Macleods and Lupin, who should be ready to supply quality-assured pretomanid 200mg tablets by early 2023.[34,35]

None of the agreements signed with Viatris, Macleods and Lupin have been made public. As highlighted earlier, these licenses on pretomanid-containing regimens for DS-TB are also linked to sublicenses on bedaquiline with Viatris and Macleods, which may have a negative impact on the availability of generic bedaquiline to treat DR-TB.

TBA is funded by governments (e.g. US, UK, Germany, Australia) and philanthropies, and was awarded a lucrative Tropical Disease Priority Review Voucher (PRV) estimated to be worth $67-350 million, by the FDA in 2019.[75,76] On these grounds, MSF has called on TBA, and its commercial pharmaceutical partner Viatris, to reduce the price of pretomanid.[77,78]

There is no justification for TBA to not be transparent about the voluntary licensing agreements it has signed with pharmaceutical companies given the significant public and collective investment and research efforts that went into the development of pretomanid.[79]

The compound patent on pretomanid expired in 2016 in the few high-income countries where it was filed, and patents were not filed in developing countries.[80,81] However, TBA has filed a patent application for the combination of bedaquiline, pretomanid and linezolid (BPaL regimen) in multiple jurisdictions, including countries with a high burden of TB such as India and Brazil.[82] Apart from the claim on the combination of the three drugs, the patent application also claims all possible dosages and treatment durations with linezolid. Given that two of the compounds of the BPaL regimen, pretomanid and linezolid, are off patent, TBA's patents on the combination are unjustified.

At the 50th Union Conference held in 2019, TBA argued that it has applied for patents to prevent "counterfeit and falsified BPaL products" coming into the market.[83] Later on, at the HIV, Hepatitis and Tuberculosis World Community Advisory Board Meeting in November 2019, TBA said it has filed for patents to "protect the drug and ensure that only companies who can ensure a quality assured product can make it". The claim that patents on BPaL products have been sought to prevent counterfeiting is disturbing and disingenuous, as it conflates quality issues with intellectual property issues. Anti-counterfeiting has been used as a patent enforcement tactic against the transit and supply of generics, affecting the availability of safe, effective and affordable medicines in LMICs.[84]

In addition, patents on this combination should not be granted as it is based on known medicines and well-known manufacturing techniques and excipients that have been used for decades in manufacturing pharmaceuticals.

# CHALLENGES TO ACCESS RIFAPENTINE-BASED FORMULATIONS FOR TPT AND DS-TB IN ADULTS

Rifapentine is a key component of shortened treatment regimens for latent TB infection with the WHO-recommended 3HP regimen (three months of weekly rifapentine plus isoniazid) and its alternative, the 1HP regimen for specific patients' groups (one month of daily rifapentine plus isoniazid).[85] Further controlled trial evidence is needed to clarify the role of the shortest TPT regimen for children, people with advanced HIV and pregnant women, but both regimens are already options which can clearly improve TPT coverage and completion rates. Rifapentine is also part of shortened treatment regimens currently being trialled and, crucially, of the new WHO-recommended four-month regimen for DS-TB.[86]

In 2020, nitrosamine impurities were identified in rifapentine-based medicines. A temporary limit was set as being acceptable by the FDA and recognised by other regulatory agencies as well as the WHO Prequalification Programme with a commitment from manufacturers to pursue further reduction of these impurities.[87] The risk mitigation plans implemented by pharmaceutical companies have impacted their capacity to supply the international market and remain their argument for not lowering prices.

## TPT

Since 2020, two quality-assured rifapentine/isoniazid fixed-dose combination (FDC) 300mg/300mg tablets are available from generic companies through the GDF: one from Macleods, granted GF ERP status in 2021 (now WHO-prequalified since May 2022), and another from Lupin granted GF ERP status in May 2022. As a result, the 150mg tablet of rifapentine from the originator company Sanofi is no longer the sole quality-assured source of rifapentine.

Furthermore, the availability of the FDC decreases the tablet intake for an adult from nine to three tablets weekly for three months for 3HP, and from five to three tablets daily for one month for 1HP. However, this FDC is not recommended for adolescents and children younger than 15 years. In addition, one tablet of vitamin B6 is recommended at each intake as a supplement to prevent peripheral neuropathy.

For younger children, the WHO Paediatric Anti-TB Drug Optimization team recommends the development of rifapentine 150mg dispersible tablet. An FDC may be prioritised in the future once the exact dosing needs for all age groups have been determined.[88] In the meantime, Sanofi has developed a paediatric dispersible rifapentine/isoniazid 150/150 FDC tested in the TB Clinical Trials Consortium Study 35 with outcomes anticipated by July 2023.[89]

Based on the GDF Medicines Catalogue, August 2022, the estimated cost per adult patient for 3HP and 1HP is $19 and $31 respectively when using Sanofi's rifapentine 150mg, priced at $0.25 per tablet, and taking into account the price of isoniazid.

On 1 August 2022, UNITAID, the Clinton Health Access Initiative (CHAI) and MedAccess announced an agreement signed with Macleods and Lupin which brings the cost of 3HP and 1HP to $14.25 and $19 respectively.[90,91] GDF is associated with this agreement for supply in 138 countries. In the previous deals signed by UNITAID with Sanofi in 2019 and 2021, then by UNITAID, CHAI and MedAccess in 2021 with Macleods, the cost of 3HP was $15.[92,93]

As rifapentine and isoniazid are off-patent compounds, it is urgent for donors (e.g., Global Fund, PEPFAR) and technical assistance providers to support an increased demand from countries so that competition between the two generic suppliers of rifapentine/isoniazid FDC can be incentivised beyond the existing agreements, which are limited to 138 countries. 3HP and 1HP regimens need to become as inexpensive as possible for broader TPT scale-up to meet the large global needs.

The 2018 United Nations High Level Meeting (UN-HLM) commitments to end TB include a drive to start TPT for at least four million contacts under five years of age, 20 million older contacts, and six million people living with HIV by the end of 2022.[94] About 22 million contacts have yet to be treated. Furthermore, as a result of the COVID pandemic, the number of people who were offered TPT in 2021 was slightly lower than in 2019.[1] In line with the WHO High Level Meeting of June 2021, MSF urges governments to expand outreach by giving TPT to an average of three household contacts of people with bacteriologically confirmed TB.[96]

## DS-TB

Since 2021, a four-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin has been recommended by WHO for patients aged 12 years or older as a shorter alternative to the long-standing six-month regimen with rifampicin, isoniazid, pyrazinamide and ethambutol, known as RHZE/RH. However, there are several access challenges to the four-month regimen.

Unlike the quality-assured FDCs for RHZE/RH widely available through several generic manufacturers active on the market, there is no FDC yet combining the four compounds of the four-month regimen. This leads to a pill burden of 7-10 tablets a day with the new regimen when using rifapentine/isoniazid 300mg/300mg FDC compared to four tablets a day for six months with RHZE/RH. Based on previous experience, around two years would be needed from pharmaceutical development until the market entry of a 4FDC.

Based on the GDF Medicines catalogue, July 2022, for an adult weighing less than 50kg, the four-month regimen costs around $250. It is therefore five times more expensive compared to the RHZE/RH regimen.

## CONCLUSION

The last two years represent chequered progress for diagnosing and treating TB. Disruptions due to the COVID pandemic have resulted in a fall in the number of people diagnosed with TB and an increase in deaths due to TB. However, since the onset of the pandemic, more effective and patient-friendly treatments and regimens for adults and children have become available to the TB community. Governments now have the opportunity to accelerate treatment and save more lives.

This progress has been enabled by trials leading WHO to recommend regimens combining bedaquiline, pretomanid, and linezolid with and without moxifloxacin, but it is threatened by reports of emerging resistance to bedaquiline and soon-to-be-disclosed data related to emerging resistance to linezolid.[28,29] Building effective regimens with bedaquiline, pretomanid and other compounds, while urgently solving the limited access to systematic DST, including rapid molecular diagnostic tests, is of paramount importance. While trial outcomes are awaited to better understand the added value of delamanid in shorter regimens, it remains an important compound to treat adult patients ineligible for short DR-TB regimens, as well as children.

The high prices of key medicines, patent evergreening practices and opaque and restrictive licensing arrangements by pharmaceutical corporations and TBA represent another barrier to the scale-up of these lifesaving treatments. Along with more rigorous scrutiny of patent applications (and patent oppositions where necessary), there is a need for greater transparency in licensing agreements that have a negative effect on access. These measures will facilitate the production of affordable generic DR-TB medicines that will help accelerate people's access to safe, short and effective treatment regimens.


Hameeda, 65, photographed in her home, is Iraq's first person to be cured with the new oral treatment for MDR-TB.

# ANNEX

## PATENT LANDSCAPE OF DR-TB DRUGS IN 30 HIGH-BURDEN COUNTRIES*

| Drug Compound | **Patent Status** (as of 12 September 2022) | | |
|---|---|---|---|
| | Granted | Pending | Not filed |
| **bedaquiline (patent application: WO2004011436)**<br><br>**Expiry:** 18.07.2023 | Brazil, Central African Republic, China, Congo, Gabon, India, Indonesia, Kenya, Lesotho, Mozambique, Pakistan, Philippines, Sierra Leone, South Africa, United Republic of Tanzania, Uganda, Viet Nam, Zambia | **Withdrawn:**<br>Thailand | Angola, Bangladesh, Democratic Republic of the Congo, Ethiopia, Democratic People's Republic of Korea, Liberia, Mongolia, Myanmar, Namibia, Nigeria, Papua New Guinea |
| **bedaquiline fumarate salt (patent application: WO2008068231)**<br><br>**Expiry:** 03.12.2027 | Central African Republic, Congo, Gabon, Indonesia, Kenya, Lesotho, Mozambique, Namibia, Philippines, Sierra Leone, South Africa, United Republic of Tanzania, Uganda, Viet Nam, Zambia | Pakistan<br><br>**Opposed:**<br>India, Thailand | Angola, Bangladesh, Democratic Republic of the Congo, Ethiopia, Democratic People's Republic of Korea, Liberia, Mongolia, Myanmar, Nigeria, Papua New Guinea<br><br>**Rejected:**<br>Brazil (under appeal), China |
| **bedaquiline paediatric formulation (patent application: WO2016120258)**<br><br>**Expiry:** 25.01.2036 | Central African Republic, Congo, Gabon, Indonesia | Brazil, China, Kenya, Lesotho, Liberia, Mozambique, Namibia, Philippines, Sierra Leone, South Africa, United Republic of Tanzania, Uganda, Zambia<br><br>**Opposed:**<br>India, Thailand | Angola, Bangladesh, Democratic Republic of the Congo, Ethiopia, Democratic People's Republic of Korea, Mongolia, Myanmar, Nigeria, Pakistan, Papua New Guinea, Viet Nam |
| **BPaL regimen† (patent application: WO2017066053)**<br><br>**Expiry:** 05.10.2036 | NIL | Brazil, China<br><br>**Opposed:**<br>India | Angola, Bangladesh, Central African Republic, Congo, Democratic Republic of the Congo, Ethiopia, Gabon, Indonesia, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mongolia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Sierra Leone, South Africa, United Republic of Tanzania, Thailand, Uganda, Viet Nam, Zambia |
| **delamanid (patent application: WO2004033463)**<br><br>**Expiry:** 10.10.2023 | Bangladesh, Brazil, China, India, Indonesia, Philippines, South Africa, Thailand, Viet Nam<br><br>**Opposed:**<br>Pakistan | R-Pharm | Angola, Central African Republic, Congo, Democratic Republic of the Congo, Ethiopia, Gabon, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mongolia, Mozambique, Myanmar, Namibia, Nigeria, Papua New Guinea, Philippines, Sierra Leone, United Republic of Tanzania, Zambia |

**Source:** medspal.org

* Angola, Bangladesh, Brazil, Central African Republic, China, Congo, Democratic Republic of the Congo, Democratic People's Republic of Korea, Ethiopia, Gabon, India, Indonesia, Kenya, Lesotho, Liberia, Mongolia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Sierra Leone, South Africa, Thailand, Uganda, United Republic of Tanzania, Viet Nam, Zambia; https://www.who.int/publications/i/item/9789240037021

† The BPaL regimen comprises bedaquiline, pretomanid and linezolid. No patents were filed on pretomanid and patents on linezolid have expired.

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Surayo, 30, with her 8-year-old son Zainidin, in Tajikistan's Tursunzoda district. Zainidin and his 6-year-old sister both have TB, and were diagnosed and treated by MSF.


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