ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

DR-TB & TB-PREVENTION DRUGS UNDER THE MICROSCOPE

7TH EDITION

Medicine pricing and patent issues for drug-resistant tuberculosis and tuberculosis prevention

EXECUTIVE SUMMARY

To save lives and achieve global targets, accelerating treatment and prevention of drug-resistant (DR) tuberculosis (TB) will require increased access to critical TB medicines, including bedaquiline, delamanid and pretomanid. Bedaquiline and delamanid are part of World Health Organization (WHO) recommended all-oral treatment regimens that are safer, more effective, and easier to take than past regimens. But high prices and restrictive patents on these medicines continue to be major hurdles for people's access to lifesaving DR-TB treatment. Pretomanid is recommended by WHO only under operational research conditions as part of a regimen for more complex cases.

Eight years after bedaquiline was first approved for use, and two years after WHO recommended it as a core drug for DR-TB treatment, the **price of bedaquiline** dropped to US$1.50 per day for some countries, though an estimate shows it could be priced as low as $0.25 per day. **Bedaquiline should be priced even lower and made available to more countries**, given the considerable public funding and research that went into its development. From 2015 to 2019, about 51,000 people accessed bedaquiline, only 11% of those who needed it.

Also recommended by WHO, **delamanid is one of the world's most expensive TB medicines**, at $1,700 for a 6-month treatment. With only two manufacturers controlling the market, alternative producers are needed to supply this drug at a more affordable price. From 2015 to 2019, only 3,750 people accessed delamanid.

Pretomanid, the newest approved DR-TB medicine, is one of three drugs in the BPaL regimen, along with bedaquiline and linezolid, which together form the first all-oral 6-month treatment for extensively drug-resistant TB (XDR-TB). The price of a 6-month treatment course of pretomanid is $364 through the Global Drug Facility (GDF), putting the lowest global price of BPaL at $905. However, given the public and philanthropic resources that went into pretomanid's development, **its high price is unjustified**.

TB preventive treatment (TPT) has been recommended by WHO since 1998, and today several shorter regimens are available. In 2020, WHO recommended the use of 1HP regimen in addition to 3HP, which consist of isoniazid and rifapentine, for TPT. Considering both drugs are off patent, **generic competition is required to make 3HP and 1HP regimens as inexpensive as possible for TPT scale-up**.

Along with more affordable pricing, the patent monopolies on these drugs, including **monopoly-extending "evergreen" patents and exclusive licenses, need to be strongly contested**. Close scrutiny of the novelty of secondary patent applications must be applied, and patent oppositions by the public must be enabled and supported to facilitate affordable generic production and access to lifesaving DR-TB regimens. The various patents and patent applications on key DR-TB drugs range from the basic, as in basic compound patents, to the highly unreasonable and inappropriate, in terms of pharmaceutical corporations and even non-profit organisations, such as the TB Alliance, attempting to create, defend, and extend their monopolies.

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A person living with TB swallows her daily dose of pills at Osh TB Hospital, Osh, Kyrgyzstan, August 2017

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INTRODUCTION

Tuberculosis (TB) is the world's deadliest infectious disease,[1] and drug-resistant (DR) TB is a global health emergency. The World Health Organization (WHO) has estimated that only 1 in 3 people with DR-TB is started on treatment, and those treated have faced exceedingly poor cure rates of 56% for multidrug-resistant TB (MDR-TB) and 39% for extensively drug-resistant TB (XDR-TB), as of 2018.[a,1] Before the innovations in TB over the last few years, the best DR-TB treatment entailed long regimens with painful injections, severe side effects and poor outcomes. Safer and more effective DR-TB drugs are now available for use in all-oral regimens recommended by WHO.[2,3]

In the face of poor cure rates and clear need to scale up DR-TB treatment in high-burden places, improvements in DR-TB management are finally at hand. But to achieve these improvements, the barriers to treatment scale-up must be addressed with haste, so that people with TB can benefit from these shorter, less toxic, more potent therapies. Access to testing and key DR-TB medicines, especially bedaquiline and delamanid, and potentially pretomanid, must be accelerated, including through more affordable pricing and by overcoming patent and licensing hurdles.

Also, the global COVID-19 pandemic has complicated and diverted resources from TB care, amongst other health areas. As the pandemic continues, disruption of TB services must be monitored and minimised.

This Issue Brief by Médecins Sans Frontières (MSF)'s Access Campaign examines the current landscape of DR-TB and TB-prevention drug pricing and patents, and what needs to be done to accelerate people's access to these lifesaving medicines.

Child receiving medicine as part of MSF's paediatric TB care programme in Dushanbe, Tajikistan, September 2018

PATENT OPPOSITIONS: A CRITICAL TOOL FOR ACCESS TO TB MEDICINES

Securing access to essential medical products is critical to MSF's humanitarian operations. MSF experience has shown that competition amongst quality-assured generic manufacturers is the most effective way to achieve affordable medicine prices and increase people's access to treatments. However, in many countries, MSF, health ministries and treatment providers face barriers to procuring affordable generic medicines due to monopolies caused by patents and other intellectual property.

This is why the MSF Access Campaign created the **Patent Opposition Database**,[4] an online platform to share information, resources, and provide support for challenging patents on medicines from dozens of contributing organisations and experts.

In addition to enforcing 20-year patent monopolies, pharmaceutical corporations repeatedly abuse the patent system to delay the entry of lower-priced generic competition. They often file patent applications on different forms or minor changes of the same medicine to extend the monopoly period, a practice referred to as **evergreening**. Companies may attempt to file patents on new uses or forms of a known medicine, formulations (e.g., tablets, syrups), combinations, common biological processes, known manufacturing techniques, and other routine improvements related to the medicine. Such manipulative patenting practices can be tackled by enforcing strict criteria in patent examination and facilitating patent oppositions filed by the public. Successful patent oppositions prove that the patent application does not meet patentability criteria, preventing the granting of unwarranted secondary patents. This facilitates generic competition and increases access to essential medicines.

For further resources on tackling the intellectual property barriers that block people's access to essential health tools, please see the Access Campaign's webpage on intellectual property,[5] the briefing document "Grounds for Opposing Patent Application for Bedaquiline Formulation in India",[6] and the Patent Opposition Database.[4]

[a] MDR-TB is defined as TB resistant to isoniazid and rifampicin, with or without resistance to other first-line drugs. 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).

1. TRENDS IN DRUG AND REGIMEN PRICES

The only significant advancement over the last year in affordable DR-TB drug pricing was the price reduction of bedaquiline, announced in July 2020 by Johnson & Johnson (J&J), resulting in a price of US$272 per 6 months ($1.50 per day) for 139 eligible countries, provided they procure from the Stop TB Partnership's Global Drug Facility (GDF).[7] This 'deal' from J&J is addressed in the 'Bedaquiline' chapter.

With this price reduction, the WHO standard shorter all-oral bedaquiline-containing regimen now falls below the affordable target price ceiling of $500 called for by MSF,[8] as does the South African short all-oral regimen, which includes linezolid.[b] Both have a similar price compared to the former 9-month amikacin-based regimen, which is no longer recommended in the WHO 2020 DR-TB guidelines.[2]

However, for longer MDR-TB regimens for fluoroquinolone-susceptible TB requiring 6-18 months of bedaquiline, the lowest worldwide price is still $800-1,500 per patient, though 10-20% price drops were seen from 2019 to 2020.[9] Also, longer regimens for fluoroquinolone-resistant TB requiring bedaquiline and delamanid for 20 months are still priced at $7,500, and reach $10,500 when imipenem-cilastatin is added. Price decreases were only <5% over the last year, mainly due to the unchanged high price of delamanid.

Due to the COVID-19 pandemic, no new GDF tender was launched until late September 2020. GDF prices remained stable over the past year for all DR-TB medicines, except for bedaquiline after the July 2020 announcement.

The estimated costs of long and short regimens using current WHO 2020 recommendations are presented in Table 1. All regimen prices are calculated based on GDF pooled procurement prices according to the lowest price available for each quality-assured medicine in the GDF Medicines Catalogue, July 2020.[10]

TABLE 1: PRICES OF WHO-RECOMMENDED DR-TB REGIMENS

Regimen (number of months)	**Regimen price based on lowest GDF price** 2020, US$
Longer regimens (fluoroquinolone-susceptible and -resistant)	
Lfx-Bdq-Lzd-Cfz (6) / Lfx-Bdq-Cfz (12)	1,061
Lfx-Bdq-Lzd-Cs (6) / Lfx-Bdq-Cs (12)	1,172
Lfx-Bdq-Lzd-Cfz (6) / Lfx-Lzd-Cfz (12)	805
Lfx-Bdq-Lzd-Cs (6) / Lfx-Lzd-Cs (12)	916
Lfx-Bdq-Lzd-Cfz (18)	1,282
Lfx-Bdq-Lzd-Cs (18)	1,393
Bdq-Lzd-Dlm-Cfz-Cs (20)	7,376
Bdq-Lzd-Dlm-Cfz-Cs (6) / Bdq-Lzd-Cfz-Cs (12)	3,244
Bdq-Lzd-Dlm-Cfz-Imp/Cln (6) / Bdq-Lzd-Dlm-Cfz (12)	7,590
Bdq-Lzd-Dlm-Cfz-Imp/Cln (20)	10,389
Mfx-Bdq-Lzd-Dlm-Cfz (20)	7,162
Modified shorter all-oral regimen (fluoroquinolone-susceptible)	
Bdq (6)-Lfx-Cfz-Z-H^h-E-Eto (4) / Lfx-Cfz-Z-E (5)	461
Modified shorter regimens (fluoroquinolone-susceptible) (operational research conditions)	
Bdq (6)-Lzd (2)-Lfx-Cfz-Z-H^h-E (4) / Lfx-Cfz-Z-E (5)*	478
Bdq-Lfx-Cfz-Z-H^h-E-Eto (4) / Bdq-Lfx-Cfz-Z-E (6)	620
Bdq-Lfx-Lzd-Cfz-Cs (9)	824
Bdq-Lfx-Lzd-Cfz-Z (4) / Bdq-Lfx-Cfz-Z (5)	658
Dlm-Lfx-Lzd-Cfz-Z (4) / Dlm-Lfx-Cfz-Z (5)	2,832
Bdq-Dlm-Lfx-Cfz-Lzd (6)	2,150
Shorter all-oral regimen (fluoroquinolone-resistant) (operational research conditions)	
Bdq-Pa-Lzd (6) (referred to as BPaL in 2020 WHO guidelines)	905**
Bdq-Dlm-Cfz-Lzd (9)	3,173

* Modified short regimen implemented in South Africa for routine use

** Global Drug Facility (GDF) estimate[9]

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

[b] Linezolid (2 months) + high-dose isoniazid (4) + bedaquiline (6) + levofloxacin, ethambutol, pyrazinamide, and clofazimine (9)

COUNTRIES MAKING THE SWITCH TO ALL-ORAL DR-TB REGIMENS

In December 2019, a major milestone was reached where for the first time WHO began recommending all-oral regimens, either long or short, as the preferred treatment option for people with DR-TB, with all injectable drugs removed from any preferred regimen.[11] These regimens lead to better treatment outcomes and reduce rates of severe side effects, preventing long-term disabilities.

Despite bedaquiline being one of the preferred drugs to treat DR-TB, its use has unfortunately remained severely limited. Between July 2015 and December 2019, only 51,098 people (or 11% of those who needed it) were able to access bedaquiline, and only 3,750 people were able to access delamanid.[12]

Countries should strive to keep pace with revised national policies that include these newer, safer, and more effective treatments.

2. NEW PAEDIATRIC FORMULATIONS

In May 2020, the US Food and Drug Administration (FDA) granted approval of 20mg dispersible tablets of bedaquiline for children 5 years or older and weighing at least 15 kg.[13] These became available from GDF in June 2020 at $200 for a 6-month treatment for children 5-12 years old.[14] Since August 2019, bedaquiline (adult dosage) had already been FDA-approved for adolescents 12-18 years old and weighing at least 30 kg.[15] WHO recommends bedaquiline for children 6 years and older.[2]

While delamanid is currently WHO-recommended for children 3 years and older,[2] the current 50mg adult formulation 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 years of age.

Mylan has developed dispersible formulations of 10mg and 50mg of pretomanid, though their evaluation in clinical trials is pending additional safety data requested by the FDA.[16]

WHO-prequalified (PQ) child-friendly formulations of clofazimine, cycloserine, ethambutol, ethionamide, isoniazid, levofloxacin, moxifloxacin and pyrazinamide are available through GDF (Table 2). A linezolid dispersible tablet, which only one generic company is developing, is needed, to move away from Pfizer's monopoly with their suspension formulation, the price for which is unaffordable and manufacturing irregular due to low global demand.

TABLE 2: WHO-PREQUALIFIED PAEDIATRIC DR-TB DRUG FORMULATIONS

Medicine	Formulation	Manufacturer(s)	Registration Status
Pyrazinamide	150mg dispersible tablet	Macleods MicroLabs	PQ granted December 2016 PQ granted September 2017
Ethionamide	125mg dispersible tablet	Macleods MicroLabs	PQ granted May 2017 PQ granted July 2019
Levofloxacin	100mg dispersible tablet	Macleods MicroLabs	PQ granted February 2018 PQ granted October 2019
Ethambutol	100mg dispersible tablet	Macleods	PQ granted March 2018
Cycloserine	125mg capsule	Macleods	PQ granted July 2018
Moxifloxacin	100 mg dispersible tablet	Macleods MicroLabs	PQ granted December 2018 PQ granted October 2018
Isoniazid	50mg & 100mg dispersible tablet	MicroLabs	PQ granted March 2020
Clofazimine	50mg tablet	Macleods	GF ERP granted until June 2020
Linezolid	150mg dispersible tablet	Macleods	PQ/GF ERP submission in progress
Bedaquiline	20mg tablet	Johnson & Johnson	FDA approval May 2020
Delamanid	25mg dispersible tablet	Otsuka	Available via compassionate use
Pretomanid	In development	TB Alliance / Mylan	N/A

PQ: prequalification by WHO; GF ERP: Global Fund Expert Review Panel; FDA: US Food and Drug Administration.

3. TB PREVENTIVE TREATMENT (TPT)

While TB preventive treatment (TPT) has been recommended by WHO since 1998,[17,18] there are now several shorter regimens available, leading to improved outcomes (Table 3). Short rifampicin-based regimens include 4 months of daily rifampicin (4R), and 3 months of daily rifampicin plus isoniazid (3RH). Newer rifapentine-based regimens include 3 months of weekly rifapentine plus isoniazid (3HP), and 1 month of daily rifapentine plus isoniazid (1HP). In 2020, WHO recommended both rifapentine-based regimens for TPT, including for people living with HIV.[19] These combined treatments are shorter and associated with reduced toxicity, increased treatment completion and similar efficacy to isoniazid preventive therapy (IPT), and they may be logistically easier for TB programmes to scale up.[20]

TABLE 3: TB PREVENTIVE TREATMENT (TPT) REGIMENS

TPT regimen	Frequency	Duration
Rifapentine + isoniazid (3HP)	Weekly	3 months
Rifapentine + isoniazid (1HP)	Daily	1 month
Rifampicin + isoniazid (3RH)	Daily	3 months
Rifampicin (4R)	Daily	4 months

Without yet a fixed-dose combination (FDC) for rifapentine and isoniazid, the pill burdens for 3HP and 1HP are relatively high. For 3HP, a person must take in total 9 tablets weekly for 3 months, while for 1HP, they must take 5 tablets daily for 1 month. Furthermore, one tablet of vitamin B6 is recommended at each intake as a supplement to prevent peripheral neuropathy.

For isoniazid, several WHO PQ generic versions are available. For rifapentine, generic manufacturers are developing 300mg tablets, but only one quality-assured source of 150mg is available, from the originator company Sanofi.

Macleods was granted Global Fund Expert Review Panel (ERP) approval until November 2020 for rifapentine/isoniazid FDC 300mg/300mg,[21] but this formulation is not yet on the market. This FDC is not recommended for adolescents and children younger than 15 years old. The future marketing channel for this FDC remains unclear.

At a price of $0.21 per tablet of rifapentine 150mg, and taking into account the cost of isoniazid, the estimated price of 3HP is $16 and 1HP is $26. In October 2019, Unitaid, Global Fund and Sanofi announced an agreement discounting the price of a 3-month treatment course of rifapentine 150mg alone by nearly 70%, from $45 to $15 (ex-works price), without taking into account the cost of isoniazid within the 3HP regimen.[22] This discount applied to 100 low- and middle-income countries (LMICs) burdened by TB, for a 12-month period. Renewal for 2021 will be confirmed by September 2020. Under a Unitaid agreement, a treatment course of the Macleods FDC, once it is available, will cost $15, slightly lower than with Sanofi's product. This price applies to 138 countries and will remain in effect through December 2021.[23]

As of 2018, TPT coverage for people living with HIV and for household contacts were estimated at 30% and 1.8%, respectively,[24] compared against 2022 global targets. To achieve the global target, committed to at the 2018 UN High-Level Meeting on TB, of providing TPT to at least 30 million people by 2022,[25,26] no limitations should be set on the number of countries that can access affordable rifapentine tablets or FDCs. Considering that rifapentine and isoniazid are off patent, generic competition is required to make 3HP and 1HP regimens as inexpensive as possible for broader preventive treatment scale-up.

Patent barriers and oppositions

Rifapentine and isoniazid are old off-patent medicines first used in the 1950s and 1960s and considered global public goods.[23,27] Since 2014, Sanofi has applied for patents on FDCs of isoniazid and rifapentine in 69 countries. These evergreening patents could potentially give Sanofi a monopoly on these FDC formulations until 2034, blocking entry of affordable generic versions.[27]

In December 2019, civil society groups in India[28,29] and Thailand[30] filed oppositions encouraging the national patent office to reject these evergreening patent applications trying obviously to combine old drugs. Sanofi withdrew its patent filings from India, Indonesia, and the European Patent Office, and has committed to a process of abandoning patent applications pending in Thailand, Algeria, Brazil, Chile, Colombia and Russia, where such claims are pending.

Further, Sanofi responded to a letter sent by Treatment Action Group (TAG) calling for patent withdrawals on rifapentine and isoniazid, saying "Sanofi commits not to reinstate any of the patents/applications, and not to initiate any action against any party who would like to manufacture the specific formulations of the combinations once covered by Sanofi's two patent families, before the abandonments become effective under the relevant national patent regulations."[31]

Silhe, a person living with TB, at Doris Goodwin Hospital, Pietermaritzburg, South Africa, August 2018. Silhe is enrolled in the MSF-supported TB PRACTECAL clinical trial to find shorter, less toxic, more effective treatment regimens for MDR-TB.

4. BEDAQUILINE

For the past several years, MSF has been calling on J&J to reduce the price of bedaquiline to $1 a day, a more affordable and accessible price for people in urgent need of lifesaving TB treatment.[7] Researchers have calculated that bedaquiline could be produced and sold at a profit for $0.25 per day.[32] In 2015-2019, only 51,098 people – 11% of those who needed it – accessed bedaquiline.[12]

In July 2020, J&J did announce a reduction in the price of bedaquiline to approximately $1.50 per day from GDF, but this price is reached only when a 'free goods' stipulation is factored in (Table 4).[7] The 'free goods' stipulation essentially works as follows: by agreeing to purchase commitments to treat 125,000 people, GDF is able to apply a 'buy 10, get 2 free' arrangement that results in the $1.50/day price ($272 per 6 months). This price is 32% lower than the previous lowest price of $400 for a 6-month treatment course when combined with the 'free goods' approach, and 70% and 91% lower than the prices first introduced in 2014 for low-income and middle-income countries, respectively. This new price is available to 139 countries, as determined by J&J and only available through the GDF.[9]

In addition to being highly complicated, the price reduction with 'free goods' stipulation is still not low enough, and not available to all countries. By limiting country eligibility and the procurement mechanism, high DR-TB burden countries such as South Africa and the Russian Federation are left out of this deal, unless they go through GDF. The price for the Russian Federation ($8/day) by Pharmstandard remains more than 5 times higher than the new J&J price through GDF. All other Eastern Europe and Central Asia (EECA) countries are for now on the GDF eligible list.

Also of concern is the price of the paediatric formulation, which is now more expensive than the adult formulation ($1/day from GDF for younger children who receive only half the adult dose based on bedaquiline 20mg tablets, and over $2/day for older children and adolescents who receive the same dose as adults based on bedaquiline 100mg tablets).

Generic companies have started to develop bedaquiline active pharmaceutical ingredient (API) and finished product in order to be ready for market entry by July 2023, when J&J's primary patent expires. Generic competition of bedaquiline will ease DR-TB treatment scale-up.

Despite the recent price reduction of bedaquiline, MSF has called for the price to come down even further and be extended to more countries, given especially that substantial public taxpayer funding went into the drug's development.[7]

TABLE 4: KEY DR-TB DRUG PRICES AND PRODUCERS

Medicine	Purchasing mechanism	Producer	Price per person per month, US$*	Target price for generic versions (per month)†
Bedaquiline 100mg tablet	GDF	J&J (Janssen)	$45	$8-17
	Russian Federation - government tender	Pharmstandard	$246	
Delamanid 50mg film-coated tablet	GDF	Otsuka	$283	$5-16
	South Africa - government tender	Mylan	$157[33]	
	EECA region - government tender	R-Pharm	N/A	
Pretomanid 200mg tablet	GDF	Mylan	$61	$11-35

* Lowest GDF price (multi-generic source drug)[34]

† 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 volume, competition and transparency.[32]

GDF: Global Drug Facility; EECA: Eastern Europe and Central Asia

Patent barriers and oppositions

Given the large number people who could benefit from treatment with bedaquiline-containing regimens in India, civil society there has been campaigning for the government to issue a compulsory license[c] to overcome the base compound patent barrier on bedaquiline, in order to make more affordable generic versions of the drug more available.[35]

Janssen, a subsidiary of J&J, has filed for multiple patents on bedaquiline and exerts control over the market until July 2023,[36] when its primary base compound patent expires. Given this, a number of manufacturers are preparing submissions to WHO PQ of their generic versions in anticipation of the patent expiry. However, Janssen still seeks to extend its monopoly as the patent landscape for bedaquiline shows several evergreening patents and secondary patent application filings.

Janssen has applied for secondary patents beyond the base compound on the fumarate salt form (final-product pharmaceutical formulation) of bedaquiline.[37] This could potentially extend Janssen's monopoly until 2027 in high-burden TB countries.[38,39]

[c] Compulsory licensing is the right granted by a court or designated government authority to a third party or the government itself to make use of a patent during the patent term without the consent of the patent holder, for example, for the sale, supply or procurement of generic medicines.

In India, the patent application on the fumarate salt has been challenged by networks of DR-TB survivors and people living with HIV.[6] In Brazil and Thailand, secondary patent applications on bedaquiline including the fumarate salt form were challenged in May 2020, on grounds including non-obviousness.[40] The results of these patent oppositions in these three countries are pending.

In countries where fumarate salt patent claims have already been granted (see Annex) and are difficult to revoke, generic manufacturers may face the threat of an infringement lawsuit from Janssen/J&J until the end of 2027. In such countries, governments could consider using health safeguards such as compulsory licensing to open up supply from generic manufacturers.

In addition to the patents and pending applications on the fumarate salt, Janssen also holds evergreening patents on different uses (indications), as well as different formulations. Janssen holds patents on the use of bedaquiline to treat MDR-TB[41] and latent TB,[42] a paediatric formulation,[43] and a long-acting injectable formulation.[44] 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 EECA region, to prevent a monopoly on the paediatric formulation.[45] Results are pending.

Furthermore, in India, a legal safeguard known as the Bolar exemption is critical. Bolar exemptions allow generic manufacturers to make and use patented drugs in order to prepare and complete submissions for regulatory approval and quality-assurance testing before the term of the patent expires, without risk of patent infringement.[46] Generic companies should utilise the Bolar exemption[d] for obtaining regulatory approval in India and for seeking WHO PQ and registration in high-burden countries ahead of patent expiry.

While J&J has declined to license bedaquiline to the Medicines Patent Pool (MPP),[47] the company has entered into two bilateral license agreements with TB Alliance and Pharmstandard for drug-sensitive (DS) TB and DR-TB indications, respectively. J&J's license with Pharmstandard is for manufacturing bedaquiline in the Russian Federation, and 10 other EECA countries.[48] The agreement, which is not available for scrutiny, has locked up the Russian Federation with Pharmstandard's high price of $8/day for bedaquiline. Other EECA countries can benefit from the GDF price of $1.50/day, but only if they purchase from GDF, which might not be allowed according to their national procurement rules.[7]

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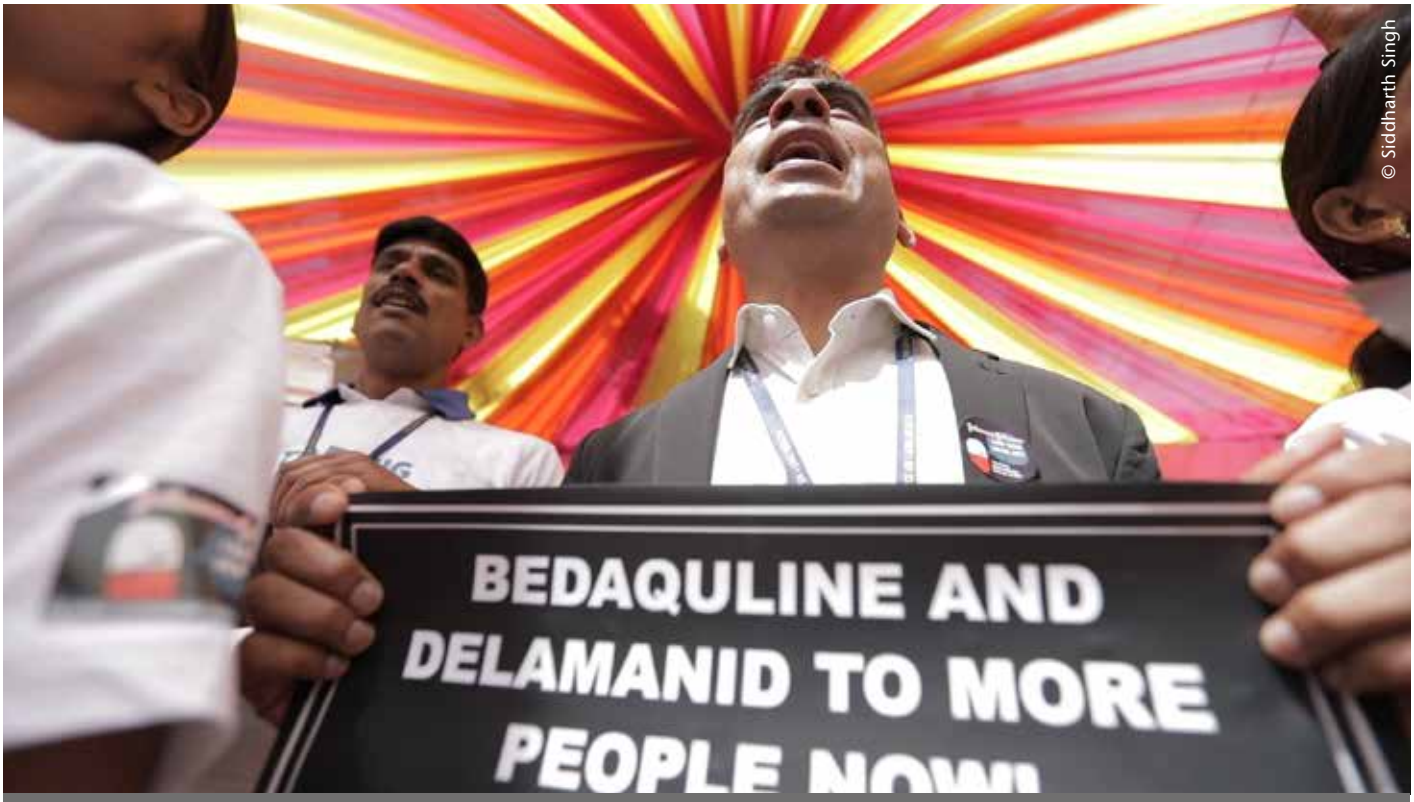
Protestors outside J&J, calling for a lower price for bedaquiline, Sao Paulo, Brazil, October 2019

[d] Seeking regulatory approval before the expiry of the patent, so that generics can enter the market as soon as the patents expire, is allowed under international and national laws.



Protestors calling for access to bedaquiline and delamanid at the 50th Union World Conference on Lung Health, Hyderabad, India, November 2019

5. DELAMANID

Delamanid is one of the most expensive DR-TB drugs recommended by WHO, at $1,700 for a 6-month treatment.[49] Since many people often need more than 6 months of treatment, the total price can become a huge financial barrier for national TB programmes.

From 2015 to 2019, only 3,750 people accessed delamanid.[12] This was likely due to the drug's high price given the lack of generic competition, relatively low registration (only 9 out of 30 high-burden DR-TB countries), and WHO classification as a Group C drug.

For countries eligible to purchase through GDF, the originator company Otsuka charges $283/month (Table 4). In South Africa, licensee Mylan charges $157/month, since June 2019.[50]

Mylan filed a registration dossier in South Africa for tablets manufactured at its Indian plant using Otsuka's spray dried powder containing the API, and plans to do so in India. By late 2021, Mylan could supply tablets fully manufactured in-house from API to finished product. This should lead to a lower price compared to the current one in South Africa, but whether this will be the case is unknown and needs to be closely followed.

R-Pharm, Otsuka's licensee for EECA countries, was granted market approval in the Russian Federation in May 2020.[51] A public price is not yet available for the Russian market, with no safeguard of how it will compare with Otsuka's current price. Russian registration was granted using the EurAsian Economic Union (EAEU) harmonised regulatory procedure.[52] Regulatory approvals may progress more rapidly in Armenia, Belarus and Kyrgyzstan since they are part of the EAEU, and R-Pharm plans registration submissions in 2020.[53]

On a positive note, WHO PQ of delamanid is proceeding, per submissions by Otsuka and Mylan.[54] WHO PQ status for delamanid would allow Otsuka and Mylan to use the WHO Collaborative Registration Procedure to speed local registration of the drug in high-burden TB countries.[55]

Patent barriers and oppositions

Delamanid is a compound whose anti-TB activity was already reported in 1993.[56] Despite this, Otsuka has filed for multiple patents on the known compound of delamanid in many LMICs.[57,58] These patents cover the basic compound;[59] API process and intermediates;[60] formulations; and even combinations with other TB drugs.[61] These patents, if granted, are due to expire between 2023 and 2031.

An analysis of the claims granted in India indicate that the basic compound patent is the only blocking patent, and the rest can be circumvented by generic producers.

The basic compound patent for delamanid is set to expire in October 2023. A number of TB manufacturers from India are likely to wait until the market for delamanid grows through an expanded indication for delamanid in any new WHO guidance, or classification of the drug as a core Group A drug, as opposed to its current limited use. These considerations will influence delamanid demand by TB programmes, and thereby determine whether generic manufacturers will proceed in filing for WHO PQ of their versions in anticipation of patent expiry.

Instead of licensing the adult formulation of delamanid to the MPP, Otsuka entered into an undisclosed deal in 2017

with Mylan for distribution in India, South Africa, and where Otsuka has no commercial presence.[62,63] The license entered by Otsuka and Mylan is not transparent to see if it is in line with public health needs or merely acts as a mechanism to manage competition for Otsuka to keep control of the market.

The arrangement between Otsuka and Mylan has limited Mylan's rights to supply, rather than produce more affordable versions, until the patent expires in 2023. Currently, Mylan can produce and supply delamanid tablets, but only using API sourced from Otsuka, which might not substantially lower the drug's price. Benefits are seen however, at least for South Africa, where Mylan charges $157/month, as of June 2019. Only towards late 2021 can Mylan produce generic delamanid, using its own API, which is about a year before the patent expiry and the expected entry of other producers.

Also, the technology transfer terms under the agreement could put additional limitations on Mylan as a licensee, and therefore a more affordable generic delamanid. Restrictive license terms may link the transfer of manufacturing know-how to contractual obligations that prevent supply of the drug 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, which has happened in other cases.[64]

Otsuka also signed a license agreement with R-Pharm in July 2017 to supply delamanid in EECA countries.[65] The terms and conditions of this deal are also not public.

In 2017 Otsuka signed a Memorandum of Understanding (MoU) with MPP to accelerate the development of paediatric formulations.[66] However, this proved an empty gesture given that to date not a single manufacturer has come forward to seek a voluntary license to develop a paediatric version. Given Otsuka's failure to license the adult formulation to the MPP and the lack of attractiveness of the small market for paediatric formulations, MSF does not expect generic manufacturers to take up delamanid until after the patent expires in 2023.

6. PRETOMANID

In August 2019, the FDA granted approval of pretomanid to TB Alliance (TBA), when used in combination with bedaquiline and linezolid (BPaL regimen) for treating adult patients with XDR-TB, or treatment-intolerant or non-responsive pulmonary MDR-TB.[67] Pretomanid under the BPaL regimen was also granted approval in India in July 2020[68] and in the European Union (EU) in August 2020.[69] Regulatory filings have been submitted in eight additional countries.[53] BPaL is the first all-oral 6-month treatment for highly resistant forms of DR-TB recommended by WHO under operational research conditions.

In October 2019, the price for a 6-month treatment course of pretomanid was announced as $364 through GDF (Table 4), making a 6-month course of BPaL regimen $1,040.[70] With the July 2020 price reduction of bedaquiline,[7] the lowest global price of BPaL regimen is now $905 through GDF.

However, researchers have estimated that generic versions of pretomanid could be produced and sold at a profit for less than $1.35/day (<$35/month, <$210 for 6 months) when the medicine reaches prescriptions to at least 108,000 patients.[32] In addition, pretomanid was developed by TBA, a not-for-profit drug-development organisation funded by governments (e.g. US, UK, Germany, Australia) and philanthropies. With pretomanid's approval, TBA was awarded a lucrative Tropical Disease Priority Review Voucher (PRV)[71] estimated to be worth $67-350 million.[72]

Considering all these factors, there is no justification for pricing pretomanid at such a high price, nor for TBA to claim unreasonable exclusivity rights over the fruit of collective investment and research efforts. MSF has called on TBA, and its commercial pharmaceutical partner Mylan, to reduce the price of pretomanid and give up its unjustified patent filings.[70]

As of May 2020, only 10 countries had accessed, or were in the process of accessing, pretomanid via GDF, in quantities to treat a total of only >400 people with XDR-TB.[73] Also, in May 2020, Mylan launched a Named Patient Access Program (NPAP)[74] through the website www.accesspretomanid.com. The NPAP is aimed for people living in countries where pretomanid is not yet registered. Unlike similar patient-access programmes for bedaquiline and delamanid however, NPAP was not providing pretomanid free of charge, as of September 2020 (the time of this writing).

WHO PQ added pretomanid to its expression of interest list in July 2020.[75] Mylan is responsible for WHO PQ submission and plans to use the WHO Collaborative Registration Procedure.

Patent barriers and oppositions

TBA led the development of pretomanid, having gained global exclusive rights following an agreement with former biotechnology company Chiron in 2002.[76] But the compound patent on pretomanid expired in 2016 in the few high-income countries where it was filed, and the patent was not filed in developing countries.[77,78]

Although two of drugs of the BPaL regimen, pretomanid and linezolid, are off patent, TBA has taken the unjustified and excessive action of filing a patent application for the BPaL formulation in multiple countries, including high-burden countries like India and Brazil.[79] TBA has argued that the reason for applying for this patent is for the sake of stewardship, so that pretomanid is not used outside this formulation, and to prevent counterfeit and falsified BPaL products.[80] However, applying for or enforcing patents under the guise of stewardship and quality assurance is hollow, as it has nothing to do with the approval of generics by the respective national medicine regulatory authority. Further, the claim that seeking patents on BPaL is to prevent counterfeiting is disturbing given that this explanation has been used in the past to disguise patent enforcement that ultimately limits medicine access.[81]

In addition, from a patentability standpoint, patents on this combination should not be granted as it is based on known compounds and well-known manufacturing techniques and excipients that are obvious. In July 2020, a patent opposition for BPaL was filed in India.[82]

TBA has not licensed pretomanid to the MPP but entered into bilateral agreements with generic manufacturers. In April 2019, TBA and Mylan entered into an undisclosed license agreement, with Mylan responsible for manufacturing, WHO PQ submission, national regulatory approvals, distribution, pricing negotiations, and tenders. The agreement signed between TBA and Mylan is not publicly available, despite a request from civil society for transparency.[83]

This lack of transparency raises important questions about the license agreement and affordable access to BPaL, not the least of which is what countries does Mylan have exclusive rights to market the drug? Even if the license provides exclusivity in high-income countries, this information should be transparently available. TBA's license with Mylan 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.[84]

Second, pretomanid is only approved as part of the three-drug BPaL regimen, along with bedaquiline and linezolid; J&J has not licensed bedaquiline to TBA or Mylan for DR-TB. This could pose a major challenge for countries to access all three drugs: national TB programmes will have to source bedaquiline from J&J, pretomanid from Mylan, and potentially linezolid from Mylan or a third supplier, making BPaL procurement overly complex.

In October 2019, TBA signed a second non-exclusive license agreement, with Macleods to manufacture pretomanid as part of BPaL and to supply it in 143 countries.[85] Macleods could be ready with a pretomanid tablet supply by 2022 with WHO PQ by 2023.

Regulatory support, such as access to clinical data, has to be made available to licensee Mylan when registering with national drug authorities. However, lacking access to the licensing agreements, transparency on these issues is limited to discussions with TBA and Mylan.

7. IN THE PIPELINE

Despite three new medicines approved for DR-TB care after 50 years, further novel classes of medicines will be needed for which the TB mycobacterium has not yet developed resistance. Only a healthy pipeline of new compounds can allow this aspiration to come true.

Eight new candidates from a new chemical class have currently reached the clinical development stage of Phase I/II clinical trials.[86] Six others are being assessed in preclinical studies. Among the compounds that have reached Phase II, telacebec, developed by South Korean company Qurient,[87] has shown interesting early outcomes for DR-TB care,[88] to be confirmed in further trials. Similar conclusions may be drawn from early research data for OPC-167832,[89,90] developed by Otsuka, which hopes to demonstrate the added value of a DR-TB regimen built around delamanid.

This clinical interest for both these compounds led to the filing of patent oppositions by an NGO and a TB patient advocate in India in early July 2020.[91,92] The objective is to secure upfront the possibility for Indian generic manufacturers to freely produce and supply what could become key DR-TB medicines without barriers from unjustified patents.

TB IN THE TIME OF COVID-19

As the global COVID-19 pandemic continues to upend communities across the world, its impact on other public health areas is being acutely felt in MSF programmes everywhere. People with TB face limitations in accessing health services due to lockdowns and other restrictions, and TB care services are reduced in some places as resources shift to responding to COVID-19.[93,94] These factors risk increasing TB transmission, morbidity and mortality, due to delays in TB diagnosis, treatment and prevention.

In an April 2020 survey of 20 high-burden countries, at least 40% of national TB programmes reported that TB facilities were being used for COVID-19 response; and in India, daily TB notifications declined by approximately 80% during the lockdown period compared to the daily average.[95]

Timely TB diagnosis risks being weakened if Cepheid's production of Xpert MTB testing cartridges is displaced by ramped-up production of Xpert Xpress SARS-CoV-2 cartridges for COVID-19 testing. To avoid potential supply ruptures of TB tests, manufacturers should not displace their production in favor of more profitable COVID-19 tests. In South Africa, restrictions in movement led to a reduction in weekly Xpert TB positive tests of 33%,[96] and MSF expressed concern that 50% fewer patients had been diagnosed with DR-TB during lockdown measures.[97]

Data are currently limited regarding the direct impact of COVID-19 on people living with TB. Initial data from South Africa have shown a 2.5-fold increase in mortality risk for people with current TB, and 1.5-fold risk increase for people with previous TB.[98] A modelling study suggests that limited access to TB diagnosis during the pandemic in high-burden settings can increase TB-related deaths by up to 20% over 5 years.[93] However, COVID-19 response activities may present unique opportunities to put in place broader, long-term improvements in TB services, such as increased home-based care, strengthened community and self-administered treatment, further decentralised medication pick-up, more telephone consultations, and stigma reduction campaigns.[99]

CONCLUSION

The global TB community finally has promising tools and policies in hand to dramatically improve – and save – the lives of millions of people with DR-TB. But we risk "snatching defeat from the jaws of victory" if we do not scale up WHO-recommended treatment regimens with great haste. The multiple barriers to accessing essential TB medicines must come down, including high prices and restrictive patents.

In the past year, only one major advancement in DR-TB drug access was made with the price reduction of bedaquiline to $1.50 per day, with a slew of limitations and conditions. Despite this encouraging development, bedaquiline should be priced even lower and made available to more countries, given the considerable public funding that went into its development. Another essential medicine recommended by WHO, delamanid, is currently one of the most expensive DR-TB drugs; without a lower price, alternative producers are needed to affordably provide it. The newest approved drug pretomanid is part of the first all-oral 6-month treatment regimen for highly resistant forms of DR-TB recommended under operational research conditions by WHO; however it also has a high price and potential patent restrictions that may prohibit broader access.

Along with more affordable pricing, strongly countering restrictive patent practices on these and future drugs is needed, by applying strict criteria in patent examination and enabling patent oppositions by the public. This will help facilitate the procurement of essential DR-TB medicines by treatment providers, humanitarian organisations and governments – to ultimately get these lifesaving treatments to the people who need them most and save more lives.

Neilam Synrem (left), who has MDR-TB, speaks with an MSF counselor, April 2019. Ms Synrem was the first person in the MSF TB programme in Manipur, India to take a combination of bedaquiline and delamanid. She started her treatment in August 2018.

ANNEX: PATENT LANDSCAPE OF DR-TB DRUGS IN HIGH-BURDEN COUNTRIES[e]

Drug Compound	Patent Status (as of 06 July 2020)[100]		
	Granted	Pending	Not filed
Bedaquiline (patent application: WO2004011436) **Expiry:** 18.07.2023	Brazil, Central African Republic, China, Congo, India, Indonesia, Kenya, Lesotho, Mozambique, Pakistan, Philippines, Russian Federation, Sierra Leone, South Africa, United Republic of Tanzania, Viet Nam, Zambia, Zimbabwe	Thailand	Angola, Bangladesh, Cambodia, Democratic Republic of the Congo, Ethiopia, Democratic People's Republic of Korea, Liberia, Myanmar, Namibia, Nigeria, Papua New Guinea
Bedaquiline fumarate salt (patent application: WO2008068231) **Expiry:** 03.12.2027	Central African Republic, Congo, Indonesia, Kenya, Lesotho, Mozambique, Namibia, Philippines, Russian Federation, Sierra Leone, South Africa, United Republic of Tanzania, Viet Nam, Zambia, Zimbabwe	Brazil, China, India, Pakistan, Thailand	Angola, Bangladesh, Cambodia, Democratic Republic of the Congo, Ethiopia, Democratic People's Republic of Korea, Liberia, Myanmar, Nigeria, Papua New Guinea
Bedaquiline paediatric formulation (patent application: WO2016120258) **Expiry:** 25.01.2036	Central African Republic, Congo	Brazil, China, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Namibia, Philippines, Russian Federation, Sierra Leone, South Africa, United Republic of Tanzania, Thailand, Zambia, Zimbabwe	Angola, Bangladesh, Cambodia, Democratic Republic of the Congo, Ethiopia, Democratic People's Republic of Korea, Myanmar, Nigeria, Pakistan, Papua New Guinea, Viet Nam
BPaL regimen[f] (patent application: WO2017066053) **Expiry:** 05.10.2036	N/A	Brazil, China, India, Russian Federation	Angola, Bangladesh, Cambodia, Central African Republic, Congo, Democratic Republic of the Congo, Ethiopia, Indonesia, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Sierra Leone, South Africa, United Republic of Tanzania, Thailand, Viet Nam, Zambia, Zimbabwe
Delamanid (patent application: WO2004033463) **Expiry:** 10.10.2023	China, India, Russian Federation, South Africa	Brazil	Angola, Bangladesh, Cambodia, Central African Republic, Congo, Democratic Republic of the Congo, Ethiopia, Indonesia, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Sierra Leone, United Republic of Tanzania, Thailand, Viet Nam, Zambia, Zimbabwe
Isoniazid/Rifapentine (3HP) paediatric (patent application: WO2015011162) **Expiry:** 22.07.2034	China, Russian Federation, South Africa	Brazil, Nigeria, Philippines, Thailand, Viet Nam **Withdrawn:** India, Indonesia	Angola, Bangladesh, Cambodia, Central African Republic, Congo, Democratic Republic of the Congo, Ethiopia, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Pakistan, Papua New Guinea, Sierra Leone, United Republic of Tanzania, Zambia, Zimbabwe
Isoniazid/Rifapentine (3HP) adult (patent application: WO2015011161) **Expiry:** 22.07.2034	South Africa	Brazil, Nigeria, Philippines, Russian Federation, Thailand, Viet Nam **Withdrawn:** India, Indonesia **Rejected:** China	Angola, Bangladesh, Cambodia, Central African Republic, Congo, Democratic Republic of the Congo, Ethiopia, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Pakistan, Papua New Guinea, Sierra Leone, United Republic of Tanzania, Zambia, Zimbabwe

[e] Angola, Bangladesh, Brazil, Cambodia, Central African Republic, China, Congo, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Democratic People's Republic of Korea, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Russian Federation, Sierra Leone, South Africa, United Republic of Tanzania, Thailand, Viet Nam, Zambia, Zimbabwe.

[f] The BPaL regimen comprises of bedaquiline, pretomanid and linezolid. No patents were filed on pretomanid and patents on linezolid have expired.

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