



DR-TB DRUGS UNDER THE MICROSCOPE

**SOURCES AND PRICES FOR DRUG-RESISTANT
TUBERCULOSIS MEDICINES**

4th Edition – March 2016



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In 1999, on the heels of Médecins Sans Frontières (MSF) being awarded the Nobel Peace Prize – and largely in response to the inequalities surrounding access to HIV/AIDS treatment between rich and poor countries – MSF launched the Access Campaign. Its sole purpose has been to push for access to, and the development of, life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.

MSF has been involved in tuberculosis (TB) care for 30 years, often working alongside national health authorities to treat patients in a wide variety of settings, including chronic conflict zones, urban slums, prisons, refugee camps and rural areas. MSF's first programmes to treat multidrug-resistant TB opened in 1999, and the organisation is now one of the largest NGO treatment providers for drug-resistant TB. In 2014, the organisation treated over 23,000 patients with TB, including 1,800 patients with drug-resistant TB.

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TABLE OF CONTENTS

DR-TB DRUGS UNDER THE MICROSCOPE

Sources and prices for drug-resistant tuberculosis medicines

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SUMMARY ANALYSIS

2	Introduction
3	DR-TB drug and regimen pricing trends
6	Barriers to access for key DR-TB drugs
9	The road to better treatment and new regimens
12	Policy recommendations
13	Methodology

DRUG PROFILES

GROUP TWO: INJECTABLES

14	Amikacin
16	Kanamycin
18	Capreomycin

GROUP THREE: FLUOROQUINOLONES

20	Moxifloxacin
22	Levofloxacin

GROUP FOUR: ORAL BACTERIOSTATIC SECOND-LINE AGENTS

24	Ethionamide
25	Prothionamide
26	Cycloserine
28	Terizidone
30	PAS and PAS-sodium

GROUP FIVE: AGENTS WITH UNCLEAR EFFICACY

32	Clofazimine
34	Linezolid

NEW DRUGS:

36	Bedaquiline
38	Delamanid

ANNEXES

40	Annex 1: Summary table of all prices
41	Annex 2: Conditions of offer, as quoted by companies
42	Annex 3: Company contacts
43	References
46	Abbreviations
47	Glossary



INTRODUCTION

This report – now in its fourth edition – analyses the barriers and factors affecting access to treatment regimens for drug-resistant tuberculosis (DR-TB), including new and repurposed drugs. We provide detailed pricing profiles of key DR-TB drugs, using manufacturer responses to standardised questionnaires and the Global TB Drug Facility website.

Access to successful DR-TB treatment remains low. World Health Organization (WHO) reports that only half of notified MDR-TB patients were successfully treated and cured in 2014, using routine treatment.¹ Encouragingly, early results from MSF and other implementers' operational research in treating extensively drug-resistant (XDR) TB using the new drugs, bedaquiline and delamanid, in combination with promising repurposed drugs, indicate that much higher cure rates can be achieved than with existing regimens (culture conversion rates between 75% and 97% are seen², compared to 26% with existing regimens¹). However, a few years after these two new drugs – bedaquiline and delamanid, the first new drugs in nearly half a century – were conditionally approved to treat TB, barely two percent of those who could benefit from these treatments have access to them.² WHO also reports on a deadly and persistent diagnostic gap: among estimated DR-TB cases, only about a quarter of people were diagnosed in 2014.¹

TB is now the leading infectious disease killer worldwide and there is a critical need for more effective and more affordable DR-TB treatment regimens. Despite individual drug price decreases, overall regimen prices remain a barrier to sufficient treatment scale up. The price for DR-TB regimens that can be obtained from the Global Drug Facility (GDF), range from US\$1,023^a – \$4,646^b for the lowest-priced regimens, as of February 2016. The full price of preferred DR-TB regimens range from about \$1,800^c to \$4,600^d. There are

additional barriers to accessing DR-TB drugs beyond their prices, including a lack of registration in many countries, not being included on national Essential Medicine Lists (EML) and a lack of appropriate country-level guidance for programmatic use.³ Even when it is possible to procure the needed drugs, they may not be indicated for TB use (e.g. linezolid and clofazimine), which contributes to a reluctance on the part of national TB programmes to incorporate the drugs into national protocols that would enable wider access.

STOP PRESS

This report went to print just before the Global Drug Facility was due to update its prices for DR-TB drugs by 1 April 2016, once the yearly manufacturer consultation was finalised. For the most up-to-date information on GDF prices for DR-TB drugs, please consult the Global Drug Facility, www.stoptb.org/gdf/drugsupply/drugs_available.asp

To increase the chance of a cure for people with DR-TB, the deadly gaps in diagnosis and access to effective, affordable, tolerable treatment options must be closed.

A smarter DR-TB medicines market can help. This requires having enough quality-assured suppliers to meet demand and to foster price-lowering competition. WHO and experts can contribute to smarter

DR-TB markets by streamlining the number of second-line drug options recommended, in line with medical outcomes, so that the market isn't unnecessarily split. Data from ongoing and pending clinical trials should help inform decisions to cull certain drugs that have onerous side effects while offering little benefit to patients, and should help with fast-tracking other new and repurposed drugs that can improve patient outcomes. GDF could better consolidate demand if there were fewer second-line drug options. WHO and experts should also work with manufacturers to better forecast demand of streamlined drug options.

With more countries relying upon domestic funds to purchase TB and DR-TB medicines, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) should implement clear transition strategies to ensure countries can secure the purchase of quality-assured first- and second-line TB medicines, even after they graduate from support. The GDF should explore ways to evolve its business model in order to bid in national public tenders for countries that purchase outside of the GDF. For countries purchasing outside of the GDF, the importance of continuing to procure and use quality-assured drugs is vital. By publishing pricing data in this report, we hope to contribute to countries' ability to negotiate the lowest procurement price possible for quality-assured DR-TB drugs. Countries that are able to obtain affordable, sustainable access to needed DR-TB drugs have a better chance of reducing the growing number of DR-TB cases.

a. Regimen of 8 months with amikacin, ethionamide, cycloserine, levofloxacin and 16 months of ethionamide, cycloserine, levofloxacin.

b. Regimen of 12 months capreomycin, prothionamide, cycloserine, moxifloxacin, PAS and 12 months prothionamide, cycloserine, moxifloxacin, PAS.

c. Regimen of 8 months capreomycin and 24 months of cycloserine, ethionamide, moxifloxacin and pyrazinamide.

d. Regimen of 8 months capreomycin and 24 months of PAS, ethionamide, moxifloxacin and pyrazinamide.



DR-TB DRUG AND REGIMEN PRICING TRENDS

CURRENT PRICES: IMPROVEMENTS, BUT CHALLENGES PERSIST

Recent reductions in the prices of most DR-TB drugs have brought preferred regimen prices down to a range of about \$1,800-\$4,600 per treatment course (without any Group 5 or new drugs included) (see Table 1). This is a marked improvement compared to our first *Under the Microscope* report in 2011, when drugs procured through the Green Light Committee (GLC)/GDF cost between \$4,400 and almost \$9,000 per patient for a standard 18-24 month treatment course.⁴ However, at up to \$4,600 per treatment course, DR-TB treatment regimens are still unaffordable, limiting countries' abilities to respond to the growing spread of drug resistance.

A key factor in DR-TB drug price decreases is the joint GFATM-GDF Expert Review Panel mechanism, which since 2009 has been successfully attracting new manufacturers of quality-assured DR-TB medicines to the market. Competition from generic manufacturers of quality-assured finished products has reduced prices for linezolid, capreomycin, and levofloxacin (See Table 2). Additional drivers of price reductions of DR-TB drugs over the past three years vary. For example, higher order volumes helped reduce the lowest global price of DR-TB drug linezolid. In the case of cycloserine, while the number of manufacturers of the finished product remains the same, there

are now more manufacturers of the active pharmaceutical ingredients (API), contributing to the drug's lower price.

Notable exceptions to the trend of decreasing drug prices are clofazimine, amikacin, prothionamide and ethionamide, whose prices have remained steady, and kanamycin and PAS-sodium, whose prices have increased since 2013. Additionally, some countries – especially middle-income countries – that purchase outside of the GFATM-GDF mechanism may still lack the competitive markets of multiple manufacturers needed to access similarly low prices. (See Box: Spotlight on linezolid in South Africa.)

TABLE 1: 2015 PRICES FOR DR-TB DRUG REGIMENS*

	Regimen dose	Lowest unit price for a quality-assured source (US\$)	Lowest cost for regimen (US\$)	Highest unit price for a quality-assured source (US\$)	Highest cost for regimen (US\$)
Capreomycin 1g vial	1 pill a day for 8 months	3.80	912.00	8.00	1920.00
Cycloserine 250mg capsule	3 pills a day for 24 months	0.19	403.92	0.60	1296.00
Ethionamide 250mg tablet	3 pills a day for 24 months	0.06	133.92	0.10	211.68
Moxifloxacin 40mg tablet	1 pill a day for 24 months	0.44	314.64	0.66	475.20
Pyrazinamide 400mg tablet**	4 pills a day for 24 months	0.02	55.58	0.02	67.68
Total cost			1820.06		3970.56

By replacing cycloserine with PAS, the price changes to...

PAS 4g sachet / PAS-sodium 60% w/w granules 9.2g sachet	2 sachets a day for 24 months	1.31	1919.52	1.69	1919.52
Total cost			3335.66		4595.08

* Prices sourced from MSF questionnaire sent to manufacturers, September 2015, and from the April 2015 GDF catalogue for TB drugs.

** Price obtained from GDF catalogue

TABLE 2: KEY DR-TB DRUGS PRICE TRENDS

Drug	Presentation	Change in # of manufacturers from 2013	Change in lowest identified price from 2013 to 2015
Capreomycin	1g powder vial	▲ number of finished product manufacturers by 3 (5 manufacturers in 2015)	▼ by 24%
Linezolid	600mg tablet	▲ number of finished product manufacturers by 1 (3 manufacturers in 2015. In January 2016, this figure went back to 2, awaiting the final assessment of the WHO Prequalification Programme for one source)	▼ by 22%
Levofloxacin	250mg tablet	No change in number of finished product manufacturers (5 manufacturers in 2015)*	▼ by 16%
Levofloxacin	500mg tablet	No change in number of finished product manufacturers (5 manufacturers in 2015)*	▼ by 25%
Cycloserine	250mg capsule	▲ number of API sources by 2 (3 sources for cycloserine API in 2015)	▼ by 52%

* The cause(s) of price drops for levofloxacin are unknown, but it is possible that these result from an increased demand for the drugs, either for a TB indication or for other uses.

SPOTLIGHT ON ACCESS TO LINEZOLID IN SOUTH AFRICA

Multiple studies have shown that inclusion of linezolid in the treatment of XDR-TB, including for people co-infected with HIV, improves culture conversion rates and treatment outcomes.^{5,6} However in South Africa, high prices charged by a duopoly of suppliers have restricted access, keeping linezolid out of reach of many XDR-TB patients.

In late 2014, at the urging of patients, clinicians, and civil society organisations, South Africa's regulatory body, the Medicines

Control Council (MCC), registered pharmaceutical company Hetero's generic linezolid. The Hetero product is marketed in South Africa through an arrangement with Sanofi. Pharmaceutical company Pfizer's linezolid product had previously held a monopoly on the market. However, this limited competition has not resulted in significant price reductions. As of November 2015, in the private market, Pfizer was selling a 600mg daily tablet of linezolid for about

\$62 (ZAR855) per pill, while Hetero's product cost about \$47 (ZAR655) per pill.⁷ Public sector prices offered by the two suppliers are discounted, but remain too high to have been accepted by national tenders. Further competition is needed to bring prices down.

In South Africa, it is significantly less expensive for MSF to import Hetero's linezolid through our own supply channels, at a price of \$7.90 per pill (ZAR109), than to source linezolid at the Sanofi and Pfizer prices offered to South African provinces, which cost 46% to 96% more, respectively.⁷ South Africa receives support from the Global Fund to Fight AIDS, Tuberculosis and Malaria, has one of the largest TB burdens in the world, and has a high demand for linezolid⁸; the South African government should be offered prices comparable to the GDF, where linezolid costs between \$5.35 and \$5.48 per pill.



NOW CURED OF XDR-TB, SIYABULELA QWAKA, 30, WAS AN EARLY RECIPIENT OF A STRENGTHENED TREATMENT REGIMEN CONTAINING LINEZOLID, THROUGH AN MSF-SUPPORTED PILOT PROGRAMME IN KHAYELITSHA, SOUTH AFRICA.

Note: All rand to dollar conversions calculated at November 2015 rates.

TARGET PRICES: OPPORTUNITIES FOR DRAMATIC FUTURE PRICE DECREASES

MSF believes that the total price for a full treatment course should be no more than \$500. However, DR-TB regimen costs remain high and variable despite the fact that prices could potentially be universally much lower if they were based on production costs plus profit margins. A recent study developed target price ranges for DR-TB drugs based on estimated costs of active pharmaceutical ingredients (API), excipients, formulation, packaging, and a reasonable profit margin (a 'cost-plus' model).⁹ The study notes that treatment courses such as the one used in the nine-month STREAM regimen, also known as the 'Bangladesh regimen' (see Glossary) (see Box: Clinical trials landscape), are currently priced between just over \$800 to more than \$1,800 per treatment course, but could be priced as low as \$100-\$400 per treatment course based on a 'cost-plus' model (see Table 3). For the individual drugs clofazimine, linezolid, bedaquiline, delamanid, and moxifloxacin, the estimated 'target' prices per patient per month (pppm) that could be achievable with robust generic competition are listed below, along with the current price available from GDF.

To move closer to these targets we need better drug forecasting at country level. WHO and GDF could play a leading role in promoting harmonised approaches across actors – including

the Global Fund and other non-governmental organisations who provide TB care – in providing technical support at country level to develop forecasts for DR-TB medicines. Other price-decreasing measures could include promoting more competition for linezolid suppliers, encouraging new generic manufacturers for clofazimine, and measures to encourage generic production of delamanid and bedaquiline, whether via voluntary licences negotiated by the Medicines Patent Pool or through the use of public health safeguards by governments seeking to foster production or access to low-cost generic versions.

In February 2016, Otsuka and the GDF announced a price of \$1,700 per treatment course, available to Global Fund-eligible countries through the GDF.³¹ Given that delamanid is just one drug that needs to be combined with multiple other drugs to form a DR-TB regimen, this price is prohibitively expensive for most high-burden MDR-TB countries and not all high burden countries are eligible for this price. In addition to the high price, the registration of delamanid remains an issue; without broad registration and an affordable price by the company, it will be difficult for countries to scale up treatment of DR-TB and ensure the people who need this drug can receive it.



JAYNA, WHO IS 28 AND A MOTHER OF THREE, IS BEING TREATED FOR XDR-TB IN THE RUSSIAN FEDERATION. FIRST DIAGNOSED WITH TB IN 2008, JAYNA HAS HAD SEVERAL RELAPSES SINCE. THIS TIME, HER TREATMENT INCLUDES BEDAQUILINE, AND AFTER JUST ONE WEEK, SHE STARTED TO FEEL BETTER. SHE IS TOLERATING THE TREATMENT WELL AND IS EXPERIENCING NO SIDE EFFECTS.

TABLE 3: TARGET VS. CURRENT PRICES FOR KEY DR-TB DRUGS

	Clofazimine	Linezolid	Bedaquiline	Delamanid	Moxifloxacin
Target price range (pppm US\$)*	6.20-16.40	4.90-12.80	8.80-16.40	3.50-8.60	3.50-9.40
Current lowest GDF price (pppm US\$)	66	161	150	283.33	13

* Price per patient per month. Source: Gotham D et al. Target generic prices for novel treatments for drug-resistant tuberculosis. 15th European AIDS Conference, Barcelona, abstract PS2/4, October 2015.

BARRIERS TO ACCESS FOR KEY DR-TB DRUGS

In addition to price barriers, several other factors impede access to new TB drugs and repurposed drugs developed for other indications that have been proven, or are thought to be, effective against TB. Barriers include a lack of clinical data, a lack of registration in countries, and a lack of a TB indication.

NEW DR-TB DRUGS

LONG-AWAITED CLINICAL TRIAL RESULTS

Bedaquiline (marketed by Janssen) and delamanid (marketed by Otsuka) were conditionally approved in 2012 and 2013 respectively based on their phase IIb clinical data, but completion and publication of phase III data are still critically important. Delamanid's phase III clinical trial completed enrolment in November 2013, with results expected in 2017. Bedaquiline's phase III clinical trial, which expands on the existing

STREAM trial¹⁰ looking at the efficacy of shorter treatment regimens, has yet to commence.

Also of great importance are the results of a long-awaited drug-drug interaction study (AIDS Clinical Trials Group's A5343 trial), to examine possible effects of the two new drugs on the heart (QT prolongation, see Glossary for additional details), which

has not started despite being planned since 2014.¹¹ To compensate for the lack of manufacturer-initiated, regimen-based clinical research, a number of trials run by NGOs, including MSF, and other non-profit product development partnerships are underway or planned to test new DR-TB regimens containing bedaquiline or delamanid¹² (see Box: MDR-TB Clinical Trial Landscape).

MSF OPERATIONAL EXPERIENCE

MSF reports positive clinical patient outcomes with bedaquiline-containing regimens and repurposed drugs in Armenia and Chechnya, Russian Federation, where we are supporting some of the largest cohorts of XDR-TB patients receiving bedaquiline in the world. Between April 2013 and March 2015, 60 patients received bedaquiline from MSF in Armenia. In the cohort of 38 patients who started before July 2014, 24 (80%) displayed sputum culture conversion at six months; in Chechnya, 27 out of 36 (75%) MSF patients who have completed six months of treatment are culture negative. Serious adverse events were reported in four patients in the Armenian cohort, one attributed to bedaquiline QT effects without clinical consequences for the patient, who completed bedaquiline treatment. Similarly successful culture conversion rates were reported for non-MSF compassionate use cohorts in France and South Africa (97% and 77%, respectively).¹³ Additional information from the cohort in South Africa demonstrated similar safety and efficacy even when bedaquiline was given in combination with antiretroviral therapy (ART) to TB/HIV co-infected people (59.3% of the cohort were TB/HIV co-infected), another sign that bedaquiline has the potential to transform DR-TB treatment in the coming years.¹⁴



“ I don't know why I got tuberculosis, people here in the mountains don't get tuberculosis. I could hardly tolerate the treatment. I was nauseous, I vomited and couldn't eat. I survived by miracle, I thought I was going to die. But after eight months the new drugs appeared and Dr Animesh said: 'You should take these drugs, you won't die'. He's a good doctor. Thanks to all of them I recovered. ”

SAPIKHAT, 53, TALKS ABOUT HER TREATMENT FOR XDR-TB, WHICH INCLUDED BEDAQUILINE. SHE LIVES WITH HER HUSBAND, A TEACHER, AND THEIR THREE CHILDREN IN A REMOTE MOUNTAIN VILLAGE IN CHECHNYA. SAPIKHAT PREVIOUSLY ENDURED MULTIPLE HOSPITALISATIONS AND LUNG SURGERY TO TREAT HER TB; SHE NOW RECEIVES AMBULATORY CARE.

SLOW SCALE UP OF ROUTINE AND COMPASSIONATE USE OF NEW DRUGS

Outside of clinical trials, approximately 700 patients have accessed bedaquiline through compassionate use and about 2,300 have received bedaquiline as part of routine use as of January 2016. Only about 180 patients have received delamanid outside clinical trials.¹⁵

It is critical that new drugs be incorporated into routine, programmatic DR-TB treatment protocols. There is clear guidance from WHO regarding how to incorporate bedaquiline and delamanid into the routine management of patients with DR-TB. For this to become a reality, there are some important barriers that need to be addressed: the drugs need to be registered in country, with countries allowing import waivers in the meantime; countries need to update their treatment guidelines to reflect the WHO recommendations; adequate pharmacovigilance systems need to be introduced; and the accompanying drugs needed to form a regimen with the new drugs need to

be affordable and available in country. These are not insurmountable hurdles and a number of countries are taking strides to ensure that patients have the opportunity to access the new drugs, particularly bedaquiline.

South Africa has committed to treating 3,000 DR-TB patients per year with regimens including bedaquiline;¹⁶ however, this target was not met in 2015, with just 1,009 patients starting treatment with bedaquiline during the year, as of November 2015. This is in part due to a delayed transition between Janssen's national compassionate use programme, which ended in December 2014, and standard procurement by provinces. Free access to bedaquiline through compassionate use ended before provinces had managed to adequately plan for the cost of bedaquiline in annual budgets,¹⁷ leading to several months' delay in starting new patients on treatment. As more facilities in South Africa gain experience initiating

DR-TB patients on bedaquiline-containing regimens, the 3,000-patient target should be achievable in 2016, with even more ambitious numbers feasible in the future.

Bedaquiline has been granted conditional or full marketing authorisation by the National Medicine Regulatory Agency (NMRA) in nine of the 27 high MDR-TB burden countries, and submission is pending in nine others. In the case of delamanid, Otsuka has received conditional approval or full marketing authorisation in Japan, South Korea, and in Europe by the European Medicines Agency, but delamanid is not registered in any high burden countries, including four countries considered to have a high burden of MDR-TB where Otsuka carried out clinical trials with the drug. To date, it has not been possible for countries to plan for widespread programmatic use of delamanid due to a lack of registration and the lack of a system to procure the drug for use.

DRUG DONATION PROGRAMMES FOR BEDAQUILINE AND DELAMANID

Janssen and Otsuka have announced drug donation programmes for bedaquiline and delamanid, respectively. In December 2014, USAID and Janssen Therapeutics announced a donation programme for bedaquiline, with the official agreement signed in March 2015. The terms of this agreement specify that 30,000 treatment courses will be donated over a four-year period to more than 100 Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)-eligible low- and middle-income countries through Stop TB Partnership's Global Drug Facility (GDF).¹⁸ In October 2015, USAID announced Georgia as the first recipient of donated bedaquiline.¹⁹

Not all countries are eligible for these donations, however. For example, South Africa is ineligible, and there appears to be a quota on the number of treatments to be supplied to Commonwealth of Independent States (CIS) countries through the drug donation programme.

In April 2015, Otsuka announced its "FightTBack Initiative" to provide donations of delamanid to 20% of diagnosed MDR-TB patients by 2020.²⁰ Despite requests for additional details about the programme, little information is publicly available eleven months later. Based on the joint announcement with GDF at the end of February 2016³¹, it remains unclear how Otsuka will implement this donation.

MSF advocates for fair commercial terms for medicines and avoids medical products donations wherever possible. However, faced with a lack of an alternative source of delamanid for patients in our TB treatment programmes, MSF exceptionally accepted a donation of 400 treatments of delamanid from Otsuka. MSF maintains that medical product donation programmes are not a solution to access challenges and present a number of complications for sustainable access to essential medicines.²¹

DRAWBACKS OF MEDICAL PRODUCTS DONATION PROGRAMMES

There are a number of reasons why donations fail to ensure sustainable access to medical products, which is widely acknowledged by medicines purchasers like MSF, international organisations like WHO, and in academic literature. Below are some of the key points of concern regarding drug donations:

- ❖ **Unsustainability:** Continued donations are entirely dependent on the choices of the donor.
- ❖ **Insufficient scale:** In general, donations can only meet a fraction of a country's disease burden.
- ❖ **Indication restrictions:** Drug indications may be overly narrow, preventing countries from using drugs in ways that meet public health objectives.
- ❖ **Inadequate consultation with recipient countries:** Donations may not meet the public health needs of recipients.
- ❖ **Country eligibility concerns:** Potential recipients may be excluded from programmes for reasons that are irrelevant to public health needs.
- ❖ **Burdensome requirements for recipients:** Programmes may impose added logistical and operational burdens to strained health systems with onerous requirements concerning pharmacovigilance, monitoring, evaluation, etc.
- ❖ **Time delays:** Lengthy donation negotiations may prolong the period in which patients cannot access the medicine.
- ❖ **Costs incurred by recipient countries:** Recipients often must bear the costs of sorting, storing, distributing, and potentially destroying expired donated medicines, ironically making ostensibly free drugs quite costly.
- ❖ **Anti-competitive impacts on drug markets:** Generic manufacturers may be dissuaded from entering a recipient country, preventing competitive generic markets from emerging.
- ❖ **Temporary 'solution':** Donations may temporarily reduce public pressure around the underlying access problems, making it harder to expand access to the drug in the future. Additionally, donations are usually time-limited, so they are inherently not durable solutions.
- ❖ **Potential distortion of rational use:** Donated, but less effective, medicines may be used over more effective medicines.
- ❖ **Market priming:** Donor recipients may be pressured to purchase a drug from the donor once the donation has ended.
- ❖ **Disincentivising future biomedical R&D:** Other firms may be disincentivised from engaging in future research and development to create improved medicines for lack of a viable commercial market.

REPURPOSED DR-TB DRUGS

Group 5 drugs (clofazimine, linezolid, imipenem/cilastatin) show promise in treating DR-TB but still lack DR-TB indications and conclusive clinical data, which leads to problems registering, procuring, importing, and dispensing these drugs for off-label use.¹³

MDR-TB INDICATED DRUGS ON THE WHO ESSENTIAL MEDICINES LIST

In April 2015, WHO released the 19th edition of its Essential Medicines List (EML). For the first time, this EML includes MDR-TB indications for bedaquiline, delamanid, and linezolid, which should spur governments to update their national EMLs.¹³ A thorough literature review allowed experts to justify the addition of linezolid to the WHO EML with a TB indication, despite the lack of registered indication for this particular disease. Although clofazimine is still

not listed on the WHO EML as a TB medicine, it is included in the WHO Prequalification Programme's invitation to manufacturers of API and Finished Pharmaceutical Products in reference to second-line anti-tuberculosis medicines.²² This should be understood by generic manufacturers as an incentive to develop clofazimine products, and to pursue WHO prequalification or registration by a stringent regulatory authority (SRA), as required by the GFATM.

INDICATION AND REGISTRATION CHALLENGES

Another major access problem is the severely limited national registration of repurposed DR-TB drugs. For example, while linezolid may be registered in some countries for other antibiotic-resistant Gram-positive bacterial infections, it cannot be registered with a TB indication

in any country due to the lack of official indication. Clofazimine is not registered anywhere with a TB indication²³, although it may be registered by 2020 in the US, following the US Food and Drug Administration's review of an orphan drug filing and specific clinical trials by Novartis. Without a registered TB indication, countries may be reluctant to incorporate Group 5 drugs into national TB management guidelines, and may even face challenges purchasing the drug for DR-TB use. Both of these medicines should be registered with TB indications as soon as possible, with a particular emphasis on registration in high MDR-TB burden countries. In the interim, countries should consider granting import waivers for these medicines that are still unregistered nationally, whenever manufacturers obtain either WHO Prequalification Programme approval or registration by a stringent regulatory authority (SRA).



THE ROAD TO BETTER TREATMENT AND NEW REGIMENS

Treatment of DR-TB is on the cusp of change, with multiple new drug trials planned or underway (see Box: MDR-TB Clinical Trial Landscape). Given the opportunity for improvement, WHO should further improve regimens by streamlining recommended treatment options, moving away from using injectable agents and drugs with poor side effect profiles (such as PAS, ethionamide and cycloserine), and proactively working with

manufacturers to ensure sufficient supply for clofazimine, linezolid and other promising drugs.

There are numerous potential regimens to treat DR-TB using drugs from four groups (Groups 2–5). While some level of customisation is needed to ensure that the patient receives the best regimen for their resistance pattern, too much variation leads to fragmentation of an already small market.^e

For example, Group 4 contains drugs from the same class, prothionamide and ethionamide, which are both thioamides²⁴ and for which there is very little evidence to support the use of one over the other. This same issue occurs with Group 4 drugs cycloserine and terizidone which are also in the same class of antibiotic. Both drugs are recommended in the WHO guidance but there is a note that terizidone has limited programme and effectiveness data compared to cycloserine.

MDR-TB CLINICAL TRIAL LANDSCAPE

A number of clinical trials are planned or underway to assess combinations of repurposed and new TB drugs for optimal treatment regimens.¹² These include:

- **STREAM I Trial:** This is a USAID-funded, Union-sponsored and Medical Research Council UK-implemented randomised clinical trial looking at a nine-month combination of existing TB drugs for the treatment of MDR-TB.²⁵ The study regimen is ethambutol, pyrazinamide, moxifloxacin and clofazimine throughout, supplemented by kanamycin, prothionamide and high-dose isoniazid in the first four months. Participating patients are randomised to the STREAM regimen or the optimised background MDR-TB regimen. The trial includes patients co-infected with HIV. Trial countries include Ethiopia, Mongolia, Vietnam and South Africa²⁵ and the results may be ready by 2018.
- **STREAM II Trial:** This phase III trial compares six-month and nine-month bedaquiline-containing regimens against the WHO recommended and STREAM I regimens. The six month regimen adds bedaquiline to the STREAM I regimen and the nine

month regimen replaces kanamycin with bedaquiline to give an all-oral regimen for MDR-TB. Enrolment is expected to begin in March 2016.

- **NEXT Trial:** This phase III trial is currently enrolling participants in South Africa to evaluate a new treatment regimen for patients with MDR-TB through an open-label, randomised, controlled trial of a six- to nine-month injection-free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high dose isoniazid, and pyrazinamide.
- **NiX TB Trial:** This phase III open-label study assessing the safety and efficacy of bedaquiline given only with other new drugs (pretomanid and linezolid) to patients with XDR-TB or treatment intolerant/non-responsive MDR-TB, including patients co-infected with HIV, is recruiting participants in South Africa.
- **GATB NC-005 Trial:** This phase II open-label partially randomised trial to evaluate the efficacy, safety and tolerability of combinations of bedaquiline, pretomanid and pyrazinamide during eight weeks of treatment in adults with newly diagnosed drug-sensitive TB (DS-TB), or bedaquiline, moxifloxacin, pretomanid and pyrazinamide for MDR-TB recruited participants, in

South Africa, Tanzania and Uganda. Recruitment has been completed.²⁶

- **STAND Trial:** A phase III study to assess the efficacy, safety and tolerability of a six-month combination of moxifloxacin, pretomanid and pyrazinamide in subjects with MDR-TB. Also has a DS-TB arm with the same regimen, but for a shorter duration. Recruitment is currently suspended.²⁷
- **TB-PRACTECAL Trial:** MSF is sponsoring this phase II-III trial, which intends to evaluate the safety and efficacy of short treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed TB drugs for adults with MDR-TB, in partnership with the London School of Hygiene and Tropical Medicine and other leading international research organisations. Recruitment is planned for spring 2016, beginning in Uzbekistan.²⁸
- **endTB Trial:** MSF is collaborating with Partners in Health (PIH) and Interactive Research & Development (IRD) as part of the 'endTB project', which will evaluate five experimental regimens containing bedaquiline and/or delamanid by enrolling 750 participants in five countries.²⁹

e. This fragmentation may be further exacerbated by duplicative options. In these cases, if the clinical evidence for these drugs is similar, there may be a positive market impact on recommending only one drug, thereby consolidating the market and allowing economies of scale that may help to reduce prices.

3P PROJECT

Today, finally, there is a relatively robust late-stage TB drug pipeline with several drugs showing promising results. Nevertheless, the TB research and development (R&D) pipeline's potential to deliver therapeutic solutions for TB and DR-TB remains insecure. The challenges of TB drug and regimen development persist, in large part, due to the way that drugs are financed and incentivised.

Relying on monopoly-based rewards to spur innovation discourages information sharing, promotes inefficient duplication and leaves us

with unaffordable single drug end products. For TB this means that the early pipeline is weak and large companies are withdrawing from TB R&D due to a perceived lack of a market. This is why MSF and partners propose the 3P (Push-Pull-Pool) Project, to deliver affordable, effective new TB treatment regimens faster.³⁰ The 3P Project uses an open collaborative approach to drug development, and novel approaches to financing and coordinating R&D through three key features: 1. The project *pushes* upfront funding to finance R&D activities (i.e. through grants); 2. The project *pulls* or

incentivises R&D through the promise of financial rewards if certain objectives are met (i.e. through prizes); and 3. The project *pools* resulting intellectual property (IP) to ensure open collaborative research and fair licensing for competitive production and affordability of the final products. Changing the model by which TB drugs are promoted and paid for can result in major public health gains with more efficiently and affordably developed treatment regimens of new drugs, which can be used in combination and without deadly delays. Learn more about the 3P Project at: www.msfacecess.org/3P

“ I was told that if I followed treatment, I would get cured. So I tried to follow treatment, I took medicines, I had intravenous fluids. I followed treatment strictly. But the medicines produced side effects, all my bones ached because of these pills, I had an allergy. ”

MOVSAR, 49, FROM NOVYE ATAGI, CHECHNYA, DESCRIBES HIS STRUGGLES WITH MDR-TB TREATMENT. DESPITE BEING TREATED FOR TB IN 2010 AND MDR-TB IN 2011, MOVSAR WAS DIAGNOSED WITH XDR-TB IN 2014. HE WAS ONE OF MSF'S FIRST PATIENTS TO BE TREATED WITH BEDAQUILINE. DESPITE BEING DIABETIC, MOVSAR TOLERATES THE NEW TREATMENT WELL AND HAS IMPROVED CONSIDERABLY.



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TABLE 4: ACCESS STATUS AND RECOMMENDATIONS FOR KEY DR-TB DRUGS

	Bedaquiline	Delamanid	Clofazimine	Linezolid
WHO EML	Yes for DR-TB	Yes for DR-TB	Yes, but for leprosy (WHO has been in discussion with Novartis since 2008 to address indication)	Yes for DR-TB
Registration	<ul style="list-style-type: none"> • Conditional approval • Restricted use pre-XDR/XDR • Registered in 9, pending in 9, of 27 high burden countries 	<ul style="list-style-type: none"> • Conditional approval • Broader recommendation than Bdq (includes MDR-TB with an increased risk of poor outcome) • Reg. in Japan, Europe, S. Korea 	Not registered for TB in any country	Not registered for TB in any country
Indication	DR-TB	DR-TB	Indication limited to leprosy	No TB indication
Lowest global price	\$150 per patient, per month (pppm)	\$283.33 ppm	\$66 (procured on a named-patient basis only) 100mg ppm	\$161 ppm
Access conditions	<ul style="list-style-type: none"> • Donation programme launched April 2015 through USAID/GDF for 30,000 treatment courses over 4 years for all GFATM-eligible countries. Quota for CIS countries • Access in Russia and select CIS countries via Pharmstandard (ex. at \$1,351/treatment course, Feb 2016 for an order in Uzbekistan) • IP barriers until 2029 that limit generic competition or development of FDCs • Not clear if Janssen will engage in bilateral or Medicines Patent Pool-led voluntary licence negotiations 	<ul style="list-style-type: none"> • International donation programme (FighTBack) announced in April 2015 to give access to 20% of all diagnosed and treated MDR-TB patients by 2020; details remain unclear; • Access to Global Fund-eligible countries at one single public price • Patent barriers (compound and secondary patents) in place until 2031 that limit generic competition or development of FDCs • Slow discussions with generic companies for potential voluntary licence 	<ul style="list-style-type: none"> • Single producer of quality-assured clofazimine • In April 2014, US FDA agreed to review a filing under orphan drug designation by Novartis for phase II clinical trial of Cfz; could possibly lead to registration with TB indication by 2020 	<ul style="list-style-type: none"> • Secondary patents could preclude importation of low-cost generics until 2021 in some countries, although likely that generic producers will challenge or ignore the secondary patents
Recommendations	<ul style="list-style-type: none"> • Proactive plan to move from donation to sustainable, affordable price ASAP, especially for MICs • A lower, single price offered to all LICs and MICs • Reduction of IP barriers through use of TRIPS flexibilities or a voluntary licence that is negotiated through the MPP • High-burden TB countries' NMRAs must prioritise registration • Janssen must prioritise high-burden country registration • Rapidly commence trials looking at combining Bdq with other new drugs and in shorter regimens • Rapidly start phase III and paediatric trials 	<ul style="list-style-type: none"> • Otsuka to clarify future donation plan(s) in the framework of the FighTBack initiative • Otsuka to publish an access plan for non-Global Fund eligible countries (e.g. Russian Federation) and those transitioning out from Global Fund support (e.g. Georgia) • Reduction of IP barriers through use of TRIPS flexibilities or a voluntary licence that is negotiated through the MPP • Otsuka rapidly pursues registration in high-burden TB countries and clinical trial countries; until then DIm should be widely accessible through compassionate use or other early access programmes • Rapidly commence trials looking at combining DIm with other new drugs and in shorter regimens 	<ul style="list-style-type: none"> • Novartis should continue pursuing a TB indication for Cfz (current outcomes expected 2020) • A better price offered to countries • Tech transfer for API production to allow sustained availability; prioritise reformulation to a presentation more suited to hot and humid environments, and allowing dosing adaptation • Current and future generic manufacturers of active pharmaceutical ingredients and finished product of Cfz should pursue WHO prequalification • Inclusion on the WHO EML for TB 	<ul style="list-style-type: none"> • Pfizer, Hetero register Lzd in all high-burden TB countries as a priority • Quality-assured suppliers offer prices on par with GDF prices to all high-burden countries that procure linezolid outside of GDF channels • Macleods pursue the assessment of its linezolid with WHO PQ • Countries update their national EML with Lzd for TB based on the April 2015 WHO EML update • Manufacturers pursue a TB indication for this drug using the literature review gathered by the WHO EML expert committee • New generics companies (US FDA tentatively approved) register Lzd in high burden TB countries • Civil society and GDF push for more competitors to improve affordability and price transparency • A better price offered to countries • Use TRIPS flexibilities to remove secondary patents in countries where treatment scale up is needed and where secondary patents may interfere with entry of generics

POLICY RECOMMENDATIONS

People affected by TB and their treatment providers need affordable access to medicines in the most effective, safe, and tolerable regimens possible. Drug pricing, indication, registration, inclusion in the EML and national treatment guidelines, clinical data gaps, and insufficient R&D persist as barriers to improved and more affordable treatment of this centuries-old, but curable, infectious disease that kills 1.5 million people per year. Governments, donors, drug companies and health actors should be working to solve these challenges for sufficient TB and DR-TB treatment scale up.

AFFECTED COUNTRY GOVERNMENTS SHOULD:

- ❖ Scale-up optimal TB and DR-TB treatment, including use of Group 5 medicines, per WHO recommendations;
- ❖ Register Group 5 TB medicines (linezolid, clofazimine, imipenem/cilastatin) and new drugs bedaquiline and delamanid, and in the meantime allow import waivers for these medicines;
- ❖ Update national treatment guidelines and national EML to match the latest WHO recommendations;
- ❖ Ensure adequate planning and funding so that all diagnosed drug-resistant patients (MDR- and XDR-TB) are started on treatment with DR-TB medicines that are compliant with WHO quality standards;
- ❖ Set-up adequate regulations for compassionate use or expanded access programmes for new pre-registered drugs; and
- ❖ Exercise full use of public health flexibilities enshrined in international intellectual property rules for pharmaceuticals, as well as other measures available to promote competition and improve access and affordability for key DR-TB medicines.

THE GLOBAL FUND TO FIGHT AIDS, TUBERCULOSIS AND MALARIA SHOULD:

- ❖ Encourage countries to upgrade national guidelines to meet WHO recommendations; and
- ❖ Allow countries to carry on procuring quality-assured TB medicines at the lowest possible price once they transition out from GFATM support.

THE GLOBAL DRUG FACILITY SHOULD:

- ❖ Push for alternative quality-assured supplier(s) for clofazimine (2015-2016);
- ❖ Promote more competition for linezolid suppliers;
- ❖ Promote best practices on drug forecasting at country level, in order to provide manufacturers with clearer volumes to be ordered with the objective of driving down prices of DR-TB medicines; and
- ❖ Explore options allowing GDF bidding to national public tenders.

WORLD HEALTH ORGANIZATION SHOULD:

- ❖ Pursue data collection which could lead to the addition of clofazimine to the WHO EML list (Q1 2017);
- ❖ Promote fast track registrations of Group 5 medicines for TB (e.g. WHO PQ collaborative registration for prequalified medicines but also for those registered by SRAs); and
- ❖ Provide guidance on whether Group 4 drugs can be streamlined, such as recommending only one drug from each class where there are currently two drugs in the same class. (e.g. prothionamide/ethionamide, terizidone/cycloserine).

DONORS SHOULD:

- ❖ Support countries' upgrading of national TB programmes' guidelines and national EML to meet WHO recommendations; and
- ❖ Ensure that DR-TB drugs procured with donor funding are compliant with WHO quality standards.

PHARMACEUTICAL COMPANIES SHOULD:

- ❖ Submit for registration Group 5 TB medicines (linezolid, clofazimine, imipenem/cilastatin) and new drugs bedaquiline and delamanid in all high-burden countries;
- ❖ Pfizer and Sanofi should immediately offer more affordable prices for linezolid in South Africa;
- ❖ TB Alliance should develop a compassionate use program for pretomanid;
- ❖ Offer affordable, sustainable commercial prices, not limited to countries' income tiers, and where applicable, negotiate non-exclusive, broad voluntary licences with the Medicines Patent Pool. Problematic donation programmes are not a sustainable answer to access to drugs; and
- ❖ Refer to Table 4 for additional drug-specific recommendations.

CIVIL SOCIETY SHOULD:

- ❖ Ensure countries are procuring quality-assured medications for DR-TB programmes; and
- ❖ Pressure governments to upgrade national policies, including ensuring that treatment guidelines and EML are in line with WHO recommendations.

ALL STAKEHOLDERS SHOULD:

- ❖ Support the 3P Project, an alternative model of TB drug development that promotes more efficient, more effective and more affordable TB treatment regimens.



METHODOLOGY

This report looks at the sources and prices of anti-tuberculosis medicines classified in World Health Organization's (WHO) Groups 2 (injectable agents), 3 (fluoroquinolones), 4 (oral bacteriostatic second-line agents), and 5 (agents with unclear efficacy) TB medicines, and new medicines for which an interim policy guidance was recently granted by WHO, such as bedaquiline and delamanid.

DATA COLLECTION

Questionnaires were sent to companies listed on the Global Fund List of Tuberculosis pharmaceutical products,ⁱ producing at least one anti-tuberculosis product either listed on the WHO List of Prequalified Medicinal Products or approved by a stringent regulatory authority (SRA) or temporarily approved by the Expert Review Panel (ERP) of the Global Fund. The data were collected up to September 2015.

PRICE INFORMATION

Prices are listed where manufacturers agreed to share information.

A number of manufacturers, including:

- Bayer, Glenmark, Ipca did not wish to contribute to the publication;
- Hisun, Lupin, Meiji, Microlabs, Mylan, Novartis, Pfizer, Panpharma, Reimser-Fatol, Otsuka and Teva did not have prices available or did not agree to publish prices;
- no response was received from Medochemie; and
- no contact for Biocom was available.

Prices are given in US dollars (US\$), rounded up to the nearest third decimal point, and correspond to the lowest unit price (i.e. the price of one tablet, capsule or vial). When prices that varied according to packaging (e.g. blisters or bottle) were received from a manufacturer for the same formulation, the lowest price was selected. Prices listed are 'ex-works' except for prices provided by Apotex (CIF, Toronto, Canada) - see Annex 2

for details, and the Glossary for an explanation of incoterms.

The prices listed in this publication are the ones provided by the manufacturers. The prices paid by the purchaser might be higher because of add-ons (such as import taxes and distribution mark-ups), or may be lower after negotiations or as a result of effective procurement procedures.

Prices offered by the Global Drug Facility (GDF) pooled procurement mechanism are also 'ex-works' and correspond to the lowest and highest prices referenced per medicine on GDF website.ⁱⁱ Note that prices in the GDF price catalogue can fluctuate during the year if, for example, a long-term agreement with different suppliers comes to an end. In addition, this year a range of prices is provided per medicine without specific figures per manufacturer.

QUALITY INFORMATION

Products that are either listed on the WHO List of Prequalified Medicinal Products or approved by a stringent regulatory authority are listed in the price tables as '**approved**'. Products that are undergoing review by either WHO Prequalification, by a stringent regulatory authority, or that have been reviewed and listed by the ERP of the Global Fund, are listed in the price tables as '**under evaluation**'. Products that have not yet been submitted to WHO Prequalification or to a stringent regulatory authority have not been included.

Submissions to WHO Prequalification are confidential and all companies mentioned that have a dossier accepted for review have given MSF the permission to disclose this information. As the information on the WHO List of Prequalified Medicinal Products is updated regularly, the list should be consulted for up-to-date information.ⁱⁱⁱ

Products procured by GDF comply with the GDF's Quality Assurance policy.^{iv} This deems eligible for GDF procurement all products that are included on the WHO List of Prequalified Medicinal Products, that are approved by a stringent regulatory authority, or that are approved by the joint GDF/Global Fund Expert Review Panel (ERP).

The ERP is an independent technical body whose purpose is to review the potential quality risk of using medicines which are not yet WHO-prequalified or authorised by a stringent regulatory authority, and give advice to the Global Fund and the Global Drug Facility whether time-limited procurement of such products can be authorised. The list of ERP reviewed products for tuberculosis can be consulted on The Global Fund website.^v

STOP PRESS

This report went to print just before the Global Drug Facility was due to update its prices for DR-TB drugs by 1 April 2016, once the yearly manufacturer consultation was finalised. For the most up-to-date information on GDF prices for DR-TB drugs, please consult the Global Drug Facility, www.stoptb.org/gdf/drugsupply/drugs_available.asp

i. <http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/>

ii. http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

iii. <http://apps.who.int/prequal/>

iv. http://www.stoptb.org/gdf/drugsupply/quality_sourcing_process.asp

v. http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/#A_B



AMIKACIN (Am)

GROUP 2

GENERAL INFORMATION

- Therapeutic Class: Aminoglycoside antibiotic.
- ATC Code: J01GB06.³⁶
- Included in the WHO Guidelines as a Group 2 injectable agent.³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: solution for injection – 500mg/2ml; 100mg/2ml. As powder for injection – 100mg, 500mg & 1g.
- First approved by US FDA: The date of the original New Drug Application (NDA) is not publicly available on the US FDA website. The first Abbreviated New Drug Application (ANDA) was approved on 22 January 1981.³⁹
- Approved indication in the US: Amikacin is indicated for the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including bacterial septicaemia (including neonatal sepsis), serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft tissue; intra-abdominal infections (including peritonitis); burns and post-operative infections (including post-vascular surgery).⁴⁰

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Cadila	Cipla	Pharmatex	Vianex	GDF pooled procurement
Quality status	Under evaluation by WHO PQ	WHO PQ approved	SRA approved	SRA approved	GDF Quality Assurance Policy
500mg/2ml solution for injection	0.980	1.600	0.678	2.500	0.678 - 0.805

SPOTLIGHT ON ACCESS ISSUES

There is little clinical difference between kanamycin and amikacin. As they have similar side effect profiles and show high levels of cross-resistance, factors including price, availability and adaptability of formulations will influence national TB programmes or treatment providers when selecting these drugs.

Capreomycin should be used if aminoglycosides are contra-indicated or poorly tolerated; may be effective in cases showing resistance to amikacin and kanamycin.

Number of quality sources

There are several stringent regulatory authority-approved sources of amikacin. In 2011, a generic source of amikacin (Cipla) was prequalified by WHO for the first time. An additional three products are currently undergoing WHO prequalification, including a 1g/vial and a 500mg/vial.

Suitability for use in developing country settings

Amikacin, like other aminoglycosides and capreomycin, cannot be administered orally and is usually given intramuscularly (IM) but can be given intravenously (IV). This imposes

burdens both on patients and treatment programmes, as qualified staff need to administer the product.

Amikacin is available in both powder and liquid formulations; the latter is more adaptable to resource-limited settings as reconstitution is not required.

Paediatrics

Amikacin is licensed for use in neonates, infants and children.

There is a smaller dosage (100mg/2ml) available which allows for more accurate dosing in children. This formulation is not part of the portfolio of any

manufacturer contacted for the publication. There is at least one stringent regulatory authority-approved source available (e.g. Bristol-Myers Squibb) but it is not available through the GDF.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on pharmacokinetic profiles, the potential for drug interactions are low. However, there is potential for additive toxicities, in particular with antiretrovirals which may cause renal toxicity, such as tenofovir. Further studies are required to confirm this.



KANAMYCIN (Km)

GROUP 2

GENERAL INFORMATION

- Therapeutic Class: Aminoglycoside antibiotic.
- ATC Code: J01GB04.³⁶
- Included in the WHO Guidelines as a Group 2 injectable agent.³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: solution for injection – 1g/4ml. As powder for injection – 1g/vial.
- First approved by US FDA: The date of the original New Drug Application (NDA) is not publicly available on the US FDA website. The first Abbreviated New Drug Application (ANDA) was approved on 13 February 1973. The only currently registered product in the US was approved on 17 November 2002.
- Approved indication in the US: Kanamycin is indicated in the short-term treatment of serious infections caused by susceptible strains of micro-organisms.⁴¹

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Macleods	Meiji	Panpharma	GDF pooled procurement
Quality status	Under evaluation by WHO PQ	SRA approved	SRA approved	GDF Quality Assurance Policy
1g powder for injection	1.000	xx	Manufacturer did not agree to publish prices	1.000- 1.721
1g/4ml solution for injection	xx	Manufacturer did not agree to publish prices	xx	2.560

SPOTLIGHT ON ACCESS ISSUES

There is little clinical difference between kanamycin and amikacin. As they have similar side effect profiles and show high levels of cross-resistance, factors including price, availability and adaptability of formulations will influence national TB programmes or treatment providers when selecting these drugs.

Capreomycin may be effective in cases showing resistance to kanamycin.

Number of quality sources

In the past, kanamycin formulations from several different manufacturers were registered in the US. However, as Fresenius Kabi has discontinued production, only two kanamycin sources are currently approved by a stringent regulatory authority: Meiji (in Japan) and Panpharma (approved in Latvia and Lithuania). Panpharma and Meiji did not agree to having their prices published. Meiji noted that all supply goes through GDF.

No sources of kanamycin are WHO-prequalified, although one manufacturer (Macleods) disclosed that they have submitted a dossier for WHO prequalification for the 1g/vial and 500mg/vial formulations which are currently under review. A price was available in September 2015 from Macleods only for the 1g/vial. Two additional sources for 1g/vial and three additional sources of 500mg/vial are undergoing WHO prequalification.³³

The supply of kanamycin remains vulnerable, with only two sources (Panpharma and Meiji) available for TB procurement, both of which have experienced production limitations. Panpharma resolved issues with active pharmaceutical ingredient (API) production which had resulted in an interruption of supply to several national TB programmes in 2010, although production only resumed in late 2011. Meiji was identified by

GDF as an alternative source in 2010; however their limited production capacity means availability of kanamycin is insufficient to cover global needs. Further challenges in the production of the active ingredient occurred in 2015 requiring extra manufacturing steps to ensure the sterility of the API, leading to delays in supply and a 21% increase in the price of the finished product.

Additional manufacturers exist in China, India, in countries from the former Soviet Union, and in other countries, but it is unknown whether they comply with WHO quality standards.

Active Pharmaceutical Ingredient

Issues with the production of the API remain a barrier in increasing the number of quality-assured sources for the finished product.

Kanamycin API is manufactured by a specialised process of fermentation. There are few manufacturers globally who have the capacity to produce quality-assured API through this fermentation process, and the complexity is further increased as the API should be sterile. The quality assurance of the API is a key factor and is often what prevents companies from securing approval of the finished product through WHO Prequalification or a stringent regulatory authority.

Suitability for use in developing country settings

Kanamycin, like other aminoglycosides and capreomycin, cannot be administered orally and is usually given intramuscularly (IM) but can be given intravenously (IV). This imposes burdens both on patients and treatment programmes, as qualified staff need to administer the product.

Kanamycin is available in both powder and liquid formulations; the latter is more adaptable to resource-limited settings as reconstitution is not required.

Paediatrics

The safety and efficacy of kanamycin in children has not been established.

While dosages are published in several guidelines^{42,43}, there is need for further research (in pharmacokinetics, pharmacodynamics and safety data) into the use of this drug in younger populations, in particular in children aged under five years.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on pharmacokinetic profiles, the potential for drug interactions are low.

However, there is potential for additive toxicities, in particular with antiretrovirals which may cause renal toxicity, such as tenofovir. Further studies are required to confirm this.



CAPREOMYCIN (Cm)

GROUP 2

GENERAL INFORMATION

- Therapeutic Class: Polypeptide antibiotic.
- ATC Code: J04AB30.³⁶
- Included in the WHO Guidelines as a Group 2 injectable agent.³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: 1g powder for injection.
- First approved by US FDA: 2 June 1971.⁴³
- Approved indication in the US: Capreomycin is to be used concomitantly with other appropriate anti-tuberculosis agents; it is indicated for use in pulmonary infections caused by capreomycin-susceptible strains of *M. tuberculosis* when the primary agents (isoniazid, rifampicin, ethambutol, aminosalicylic acid, and streptomycin) have been ineffective, or cannot be used because of toxicity or the presence of resistant tubercle bacilli.⁴³

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Akorn	Aspen	Hisun	Macleods	Vianex	GDF pooled procurement
Quality status	SRA approved	WHO PQ approved	WHO PQ approved	Under evaluation by WHO PQ (ERP approved until 31/10/2016)	SRA approved	GDF Quality Assurance Policy
1g powder for injection	8.000	8.100	Manufacturer did not agree to publish prices	4.150	6.000	3.800 - 4.700

SPOTLIGHT ON ACCESS ISSUES

Capreomycin shows moderate cross-resistance to amikacin and kanamycin and can be used when there is resistance to either one of these drugs.

With PAS and linezolid, capreomycin remains one of the three medicines which weigh heavily in the overall cost of a DR-TB regimen.

Number of quality sources

There are currently five quality-assured sources available: Akorn, who bought Eli Lilly's US licence; Vianex, a manufacturer based in Greece, received stringent regulatory authority approval in Spain in 2011; Hisun, a China-based manufacturer, received WHO prequalification in 2014; Macleod's, which received ERP approval in 2014; and Aspen, which received WHO prequalification in December 2015.

With five quality-assured sources now available for TB procurement, the supply of capreomycin has improved and the price has decreased by nearly a quarter (24%) since 2013. Two further companies have submitted a dossier for WHO prequalification.

Evolution in price

For a number of years, Eli Lilly subsidised the price of capreomycin for GLC-approved programmes, charging US\$1.02 per vial until a set volume had been ordered, and \$4.00

per vial thereafter. The price at which countries can procure capreomycin increased considerably since Eli Lilly stopped production and transferred technology to other companies (Aspen, Hisun, and SIA International).

GDF currently procures capreomycin at \$3.80 to \$4.70 per vial. Even with new quality-assured sources having entered the market, the price of capreomycin remains higher than the Eli Lilly-subsidised product, despite a price decrease of 24% since 2013.

Suitability for use in developing country settings

Capreomycin, similar to amikacin and kanamycin from the aminoglycosides class, cannot be administered orally and is usually given intramuscularly (IM), but can also be given intravenously (IV). This imposes burdens both on patients and treatment programmes, as qualified staff need to administer the product.

Paediatrics

The safety and efficacy of capreomycin in children has not been established.

While dosages are published in several guidelines, there is need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on pharmacokinetic profiles, the potential for drug interactions is low.

However, there is potential for additive toxicities, in particular with antiretrovirals which may cause renal toxicity such as tenofovir. Further studies are required to confirm this.



MOXIFLOXACIN (Mfx)

GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: J01MA14.³⁶
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.³⁷
- Mentioned as an alternative to levofloxacin for tuberculosis in the 19th edition of the WHO Model List of Essential Medicines.²³ Not included in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: 400mg tablet.
- First approved by US FDA: 12 October 1999.⁴⁵
- Approved indication in the US: Moxifloxacin was initially approved for the indications of bacterial sinusitis and community-acquired pneumonia. This was further expanded to include acute bacterial exacerbation of chronic bronchitis, uncomplicated and complicated skin and skin structure infection, and complicated intra-abdominal infections.⁴⁶

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Cipla	Hetero	Macleods	Microlabs	Sunpharma	GDF pooled procurement
Quality status	WHO PQ approved	SRA approved	WHO PQ approved	Under evaluation by WHO PQ	WHO PQ approved	GDF Quality Assurance Policy
400mg tablet	0.600	0.660	0.580	Manufacturer did not agree to publish prices	0.510	0.437-0.540

SPOTLIGHT ON ACCESS ISSUES

Moxifloxacin use is increasing due to the key role that fluoroquinolones play in the treatment of drug-resistant forms of tuberculosis.

Based on 2011 WHO DR-TB programmatic guidelines, the use of later generation fluoroquinolones, such as moxifloxacin and levofloxacin, are preferred to ofloxacin (inferior performance and higher risk of resistance). There is, however, potential for cross-resistance between the later generation fluoroquinolones.

Number of quality sources

Bayer was the only quality-assured source of moxifloxacin available for many years. In November 2010, Cipla's product became the first generic moxifloxacin to be prequalified by WHO, and in 2013 two more sources (Macleods and Sun Pharmaceuticals) were prequalified. One additional source (Hetero) is SRA approved. Currently seven manufacturers are under evaluation by WHO PQ.

With additional quality-assured sources entering the market, access to moxifloxacin appears to be relatively secure for the time being. Prices, which in the past represented a barrier to access, are continuously decreasing; since 2013, the lowest price on the market has decreased by 27%.

Approved indication

While moxifloxacin has been shown to be effective against *M. tuberculosis* and has been included in many treatment guidelines for DR-TB, it has not yet received an approved TB indication by any stringent regulatory authority.

Patents

In India, the Markush and compound patent applications were not eligible for product patents under the 1970 Patent Act, and the crystal monohydrate form was rejected after a pre-grant opposition was filed by Ranbaxy Laboratories. As a result, the drug has been in generic production in India for several years and is registered by a number of generic manufacturers

with the Indian Central Drugs Standard Control Organisation, a number of whom have filed and obtained WHO pre-qualification and/or US FDA approval.

The basic Markush and compound patents which covered the moxifloxacin molecule have started to expire around the world, and generic companies have worked around the secondary patents on the crystal monohydrate form⁴⁷ and the process of preparing an oral tablet formulation.⁴⁸ As a result, generics are now available in the US (launched in February 2014)⁴⁹, Canada and South Africa. Generic versions have now been registered in South Africa and are supplied for DR-TB treatment through the national TB programme as part of the government tender awarded in 2011. Generic versions are also marketed in the Russian Federation.

Paediatrics

The safety and efficacy of moxifloxacin in children has not been established.

While dosages are published in several guidelines^{42,43}, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years. Existing studies show substantially lower serum concentrations in children compared to adults at the currently recommended doses, probably due to faster elimination.⁵⁰

As there is no paediatric formulation available, paediatric doses are

obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many resource-limited settings where DR-TB is prevalent.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on the metabolism rate of moxifloxacin, levels of the drug may be reduced by the use of ritonavir and increased by atazanavir. Further research is needed to assess this.

Protease inhibitors and efavirenz may prolong QT interval, so caution is advised in concomitant use with moxifloxacin, with electrocardiogram monitoring recommended.

Oral absorption of fluoroquinolones is reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets.

Special caution

Moxifloxacin can affect cardiac conduction (QT prolongation). QT prolongation can infrequently result in a serious (rarely fatal) fast/irregular heartbeat, known as torsades de point. This is an important consideration, as several new (such as bedaquiline and delamanid) and repurposed TB drugs (clofazimine) have a similar risk, and it is unclear if this will be an additive effect. This is an effect seen in this class of drugs, but is most pronounced with moxifloxacin.



LEVOFLOXACIN (Lfx)

GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: J01MA12.³⁶
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸ Levofloxacin is considered a better alternative to ofloxacin, based on availability and programme considerations.
- Presentations available: 250mg, 500mg and 750mg tablets; 25mg/ml oral solution.
- First approved by US FDA: 20 December 1996. The paediatric formulation (25mg/ml oral solution) was approved on 21 October 2004.⁵¹
- Approved indication in the US: Levofloxacin was initially approved for the indications of acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, complicated urinary tract infections (UTI), and acute pyelonephritis. This was further expanded to include uncomplicated UTI, chronic bacterial prostatitis, and treatment of inhalational anthrax (post-exposure).⁵¹

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Apotex	Cipla	Hetero	Labatec	Macleods	Microlabs	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	SRA approved	SRA approved	WHO PQ approved	WHO PQ approved	GDF Quality Assurance Policy
250mg tablet	0.090*	0.061	0.059	1.538	0.043	0.057	0.033-0.055
500mg tablet	0.130*	0.110	0.105	2.315	0.078	0.092	0.059-0.097
750mg tablet	0.150*	xx	0.240	xx	0.128	xx	0.100

* Inconterm CIF

SPOTLIGHT ON ACCESS ISSUES

There is potential for cross-resistance between the later generation fluoroquinolones. Based on 2011 WHO DR-TB programmatic guidelines, the use of later generation fluoroquinolones, such as moxifloxacin and levofloxacin, are preferred to ofloxacin.

Number of quality sources

Levofloxacin 250mg and 500mg oral formulations produced by Cipla were prequalified by WHO in December 2011, with Microlabs following in October 2012, Apotex in June 2013 and Macleods in October 2014. Currently, an additional four manufacturers for the 250mg product, and three manufacturers for 500mg, are under evaluation by WHO Prequalification. A significant number of generic versions have been approved by stringent regulatory authorities, since patents expired in the US and in Europe in 2011.

The first 750mg formulation (produced by Apotex) was prequalified by WHO in June 2013, followed by Macleods, prequalified in October 2014.

Evolution in price

The price of levofloxacin does not appear to be an issue, and it has continued to fall over recent years.

Approved indication

The 2011 WHO programmatic guidelines for DR-TB recommend use

of later generation fluoroquinolones, including levofloxacin. However, levofloxacin does not have a TB indication approved by any stringent regulatory authority.

Patents

Patents on levofloxacin held by Daiichi Sankyo in the US and in several European countries expired in 2010.

Other patents in the US and in several European countries claiming levofloxacin expired in June 2011.

Paediatrics

The US FDA has approved levofloxacin for use in children aged over six months, but only for acute infections. The safety of levofloxacin in children treated for more than 14 days has not been studied; as this drug may be taken for up to two years, there is an urgent need for more safety data on the use of levofloxacin for extended periods in children.

While there are two manufacturers of the paediatric formulations (25mg/ml oral solution) available in the US, these are not widely available elsewhere.

Currently, the majority of DR-TB programmes prepare paediatric doses by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many resource-limited settings where DR-TB is prevalent.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on the metabolism rate of levofloxacin, no interactions are expected. However, further research is needed to assess this.

Protease inhibitors and efavirenz may prolong QT interval, so caution is advised in concomitant use with levofloxacin, with electrocardiogram monitoring recommended.

Oral absorption of fluoroquinolones is reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets.



ETHIONAMIDE (Eto)

GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Carbothionamides group, derivative of isonicotinic acid.
- ATC Code: J04AD03.³⁶
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: 250mg and 125mg tablets.
- First approved by US FDA: 30 April 1965.⁵²
- Approved indication in the US: ethionamide is primarily indicated for the treatment of active tuberculosis in patients with *M. tuberculosis* resistant to isoniazid or rifampicin, or where the patient is intolerant to other drugs.⁵²

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Cipla	Lupin	Macleods		Microlabs	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	WHO PQ approved	Under evaluation by WHO PQ (ERP approved until 02/07/2016)	WHO PQ approved	GDF Quality Assurance Policy
125mg tablet	xx	xx	xx	0.112	xx	xx
250mg tablet	0.098	Manufacturer did not agree to publish prices	0.066	xx	0.082	0.062-0.080

SPOTLIGHT ON ACCESS ISSUES

Prothionamide is the propyl analog of ethionamide. There is complete cross-resistance between the two drugs and they are used interchangeably.

Number of quality sources

The supply and number of sources of ethionamide 250mg is gradually improving, with four WHO-prequalified products available. In addition, Macleods has developed a 125mg paediatric formulation which was approved by the GDF/Global Fund Expert Review Panel (ERP) in July 2015.

Evolution in price

The price of ethionamide does not appear to be an issue.

Paediatrics

The safety and efficacy of ethionamide in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

HIV co-infection

While no antiretroviral interaction studies have been performed, pharmacokinetic profiles suggest that drug interactions with ethionamide are possible.

There is the possibility of additive toxicities with antiretrovirals which may cause hepatotoxicity, including efavirenz and nevirapine.

With the potential for interactions with some classes of antiretrovirals, there is an urgent need for further studies.



PROTHIONAMIDE (Pto) GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Carbothionamides group, derivative of isonicotinic acid.
- ATC Code: J04AD01.³⁶
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.³⁷
- Mentioned as an alternative to ethionamide for tuberculosis in the 19th edition of the WHO Model List of Essential Medicines.²³ Not included in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: 250mg tablet.
- First approved by German Federal Institute for Drugs and Medical Devices (BfArM): First marketed in Germany in the 1970s but registered in the framework of posterior registration on 14 June 2005.⁵³
- Approved indication in Germany: Treatment of all forms and stages of pulmonary and extra-pulmonary tuberculosis as second-line drug in the case of proven multidrug resistance of the pathogens against first-line drugs; treatment of diseases caused by so-called ubiquitous (atypical) mycobacteria; treatment of leprosy in the context of modified therapy regimens.⁵⁴

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Fatol	Lupin	Microlabs	Olainfarm	GDF pooled procurement
Quality status	SRA approved	WHO PQ approved	WHO PQ approved	SRA approved	GDF Quality Assurance Policy
250mg tablet	Manufacturer did not agree to publish prices	Manufacturer did not agree to publish prices	0.120	0.100	0.130-0.178

SPOTLIGHT ON ACCESS ISSUES

Prothionamide is the propyl analog of ethionamide. There is complete cross-resistance between the two drugs and they are used interchangeably.

Number of quality sources

In February 2013, Microlabs was the first manufacturer to secure WHO Prequalification for prothionamide, followed by Lupin in June 2014. There are now four quality-assured sources for the drug, given the two existing sources approved by stringent regulatory authorities (Germany's Fatol and Latvia's Olainfarm).

An additional manufacturer has submitted its dossier for WHO prequalification.

Paediatrics

The safety and effectiveness of prothionamide in children has not been established. The paediatric formulation of ethionamide should be considered instead of prothionamide.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

HIV co-infection

While no antiretroviral interaction studies have been performed, pharmacokinetic profiles suggest that drug interactions with prothionamide are possible.

There is the possibility of additive toxicities with antiretrovirals which may cause hepatotoxicity, including efavirenz and nevirapine.

With the potential for interactions with some classes of antiretrovirals, there is an urgent need for further studies.

Continued overleaf ❖❖



CYCLOSERINE (Cs)

GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Analog of D-alanine.
- ATC Code: J04AB01.³⁶
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸
- Presentations available: 250mg capsule.
- First approved by US FDA: 29 June 1964.⁵⁵
- Approved indication in the US: Cycloserine is indicated in the treatment of active pulmonary and extra-pulmonary tuberculosis (including renal disease), when the causative organisms are susceptible to this drug and when treatment with the primary medications (streptomycin, isoniazid, rifampicin and ethambutol) has proved inadequate.⁵⁵

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Cipla	Dong A	Macleods	Microlabs	Strides	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	WHO PQ approved	Under evaluation of WHO PQ	Under evaluation by WHO PQ (ERP approved until 24/07/2016)	GDF Quality Assurance Policy
250mg capsule	Price was not available at time of data collection	0.216	0.390	Manufacturer did not agree to publish prices	0.600	0.187-0.330

SPOTLIGHT ON ACCESS ISSUES

Number of quality sources

Eli Lilly, the original licence holder of cycloserine, actively engaged in technology transfer to three generic manufacturers (Aspen, Chao Center/Purdue GMP and SIA International) and ceased production in 2008.

There are currently four WHO-prequalified sources of cycloserine, including Dong A, Macleods, and Biocom, the latter having secured approval in August 2013. In addition, Cipla received WHO prequalification in December 2015, however prices for this publication were collected in September 2015 and the price for Cipla's product is not available for this edition. In addition, Chao Center/Purdue have received approval from a stringent regulatory authority but are supplying the Northern American market.

Strides received joint GDF/Global Fund Expert Review Panel temporary approval (until July 2016), making them eligible for Global Fund procurement.

Three other manufacturers have submitted dossiers for WHO prequalification.

Active Pharmaceutical Ingredient

Until 2006, the only quality-assured source for the active pharmaceutical ingredient of cycloserine was Eli Lilly. The company completed a technology transfer for the API to Indian manufacturer Shasun in 2006. Shasun API was subsequently US FDA approved in June 2008 and was WHO-prequalified in May 2013.

There are currently three API manufacturers (Dong A, Shasun and Macleods), and Enzychem of South Korea was expected to file API PQ in June 2015; this additional manufacturer will make cycloserine API supply more sustainable.

Evolution in price

In the last three years, with the arrival of more quality-assured sources of API for cycloserine, the finished product price has decreased from between US\$0.39 and \$0.78 per unit, to between \$0.19 and \$0.60 per unit. The lowest unit price for a quality-assured source of cycloserine has dropped by 52% in three years, resulting in a considerable fall in the cost of treatment regimens containing this drug.

Paediatrics

The British National Formulary provides doses for children aged 2 to 18 years, while the US FDA states that the safety and effectiveness of cycloserine in children has not been established.

There is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which may not be available in many resource-limited settings where DR-TB is prevalent.

HIV co-infection

The metabolism of cycloserine is not completely understood, and therefore interactions with antiretrovirals are unpredictable.

There is a need for more research into potential interactions between antiretrovirals and cycloserine.



TERIZIDONE (Trd)

GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Analog of D-alanine.
- ATC Code: J04AK03.³⁶
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.³⁷
- Mentioned as an alternative to cycloserine in the 2015 WHO Model List of Essential Medicines for Adults;²³ not included in the 2013 Model List of Essential Medicines for Children.³⁸
- Presentations available: 250mg capsule.
- First approved by German Federal Institute for Drugs and Medical Devices (BfArM): First marketed in Germany in the 1970s and is still in the process of posterior registration. The filing date for this process was 1 January 1978.⁵⁴
- Approved indication in Germany: Treatment of tuberculosis in adults and adolescents aged 14 years or older.⁵⁴

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Fatol	Macleods	GDF pooled procurement
Quality status	SRA approved	Under evaluation by WHO PQ	GDF Quality Assurance Policy
250mg capsule	Manufacturer did not agree to publish prices	0.850	1.588-1.666

SPOTLIGHT ON ACCESS ISSUES

Terizidone is a combination of two molecules of cycloserine, and as such has a similar mode of action as cycloserine. There is complete cross-resistance to cycloserine and, in some countries, the drug is used instead of cycloserine.

Number of quality sources

Germany's Fatol is currently the sole quality-assured source of terizidone. One additional manufacturer (Macleods) has submitted dossiers for WHO prequalification.

Additional manufacturers exist, but it is unknown whether they comply with WHO quality standards.

Paediatrics

The safety and effectiveness of terizidone in children has not been established.

While dosages are published in several guidelines^{42,43}, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

As there is no paediatric formulation available, paediatric doses are obtained by manipulating adult formulations to achieve target doses. This requires a certain level of training, supervision and resources, which

may not be available in many resource-limited settings where DR-TB is prevalent.

HIV co-infection

As terizidone is a combination of two molecules of cycloserine and the metabolism of cycloserine is not completely understood, interactions with antiretrovirals are unpredictable.

There is a need for more research into potential interactions between antiretrovirals and terizidone.



PARA-AMINOSALICYLIC ACID (PAS) and PARA-AMINOSALICYLATE SODIUM (PAS-sodium)

GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Salicylic acid anti-folate.
- ATC Code: for PAS: J04AA01³⁶; for PAS-sodium: J04AA02.³⁶
- Included in the WHO Guidelines – PAS: as a Group 4 oral bacteriostatic second-line agent; PAS-sodium: not included.³⁷
- PAS is included in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children.³⁸ PAS-sodium is not included in either document.
- Presentations available: PAS: 4g sachet. PAS-sodium: 60% weight for weight granules 9.2g sachet and 100g jar; powder for solution 5.52g sachet (equivalent to PAS 4g sachet).
- First approved by US FDA: PAS-sodium was first registered in a tablet formulation on 8 March 1950. Currently, only PAS is available in the US, with the product registered on 30 June 1994.⁵⁶
- Approved indication in the US: PAS is indicated for the treatment of tuberculosis in combination with other active agents. It is most commonly used in patients with multidrug-resistant TB or in situations when therapy with isoniazid and rifampicin is not possible due to a combination of resistance and/or intolerance.⁵⁶

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

PAS	Jacobus	GDF pooled procurement
Quality status	SRA approved	GDF Quality Assurance Policy
4g sachet	1.500	1.333

PAS-SODIUM	Macleods	Olainfarm	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	GDF Quality Assurance Policy
60% w/w granules – 9.2g sachet	1.690	xx	1.690
60% w/w granules – 100g jar	18.360	xx	18.360
Powder for oral solution – 5.52g sachet	xx	1.400	1.370

SPOTLIGHT ON ACCESS ISSUES

With capreomycin and linezolid, PAS is one of the three medicines which weigh heavily in the overall cost of a DR-TB regimen.

Para-aminosalicylate sodium (PAS-sodium) is the sodium salt of para-aminosalicylic acid (PAS), with 1.38g of PAS-sodium equivalent to approximately 1g of PAS.

Number of quality sources

There is currently only one quality-assured source of PAS (Jacobus), and two quality-assured sources of PAS-sodium (Macleods and Olainfarm), with no other sources in the pipeline.

With three quality-assured sources of PAS and PAS-sodium now available for procurement, supply has improved, but is still considered vulnerable, particularly as the different formulations available are not easily interchangeable.

Evolution in price

The price of PAS has stagnated for more than three years. The lowest price for a quality-assured source

of PAS-sodium has stagnated, while the second source price has increased by 30% since 2013. Prices of both PAS and PAS-sodium remain a concern, and no additional quality-assured sources have been identified since 2011.

Paediatrics

The safety and effectiveness of PAS and PAS-sodium in children has not been established.

While dosages are published in several guidelines^{42,43}, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

As there is no paediatric formulation available, paediatric doses are obtained by measuring the adult granular formulations. Jacobus supplies a graduated dosage scoop for PAS, and Macleods offers measuring spoons for PAS-sodium, both of which allow for a more accurate paediatric dosage. These spoons are product-specific and cannot be interchanged.

HIV co-infection

No antiretroviral interaction studies have been performed, but based on the pharmacokinetic profile of PAS, drug interactions are unlikely. Studies should be performed to confirm this.



CLOFAZIMINE (Cfz)

GROUP 5

GENERAL INFORMATION

- Therapeutic Class: Phenazine Derivative.
- ATC Code: J04BA01.³⁶
- Included in the WHO Guidelines as a Group 5 medicine (agents with unclear efficacy).³⁷
- Included in the 19th edition of the WHO Model List of Essential Medicines (as an anti-leprosy medicine)²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children (as an anti-leprosy medicine),³⁸ but not yet included for TB indication.
- Presentations available: 50mg and 100mg soft-gel capsules.
- First approved by US FDA: 15 December 1986.⁵⁷
- Approved indication in US: Clofazimine is indicated in the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum.⁵⁷

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Novartis	GDF pooled procurement
Quality status	SRA approved	GDF Quality Assurance Policy
50mg soft-gel capsule	Manufacturer did not agree to publish prices	0.547-0.713
100mg soft-gel capsule	Manufacturer did not agree to publish prices	1.095-1.267

SPOTLIGHT ON ACCESS ISSUES

Clofazimine is a Group 5 medicine which is mainly used in patients with pre-XDR-TB and XDR-TB. With no official indication for DR-TB, and owing to its effectiveness in TB having not been clearly established, in 2014 Novartis filed an Investigational New Drug application with the US FDA linked to a clinical development programme for clofazimine for a potential DR-TB indication. The 2011 WHO programmatic guidelines³⁷ recommend the use of clofazimine for patients with MDR or XDR-TB, when there are no other options available.

However, clofazimine is a key component of a shortened nine-month regimen, and recent systematic reviews suggest that clofazimine could be considered as an additional therapeutic option in the treatment of DR-TB.⁵⁸

Novartis does not make this drug available for DR-TB treatment on the basis of a lack of efficacy and safety data, and owing to concerns over liability for off-label use. Because the company donates clofazimine to WHO as part of a multi-drug co-blistered therapy for leprosy⁵⁹, Novartis did not submit a price for this publication.

As TB programmes' demand for this drug has increased, WHO has been in discussion with Novartis since 2008⁶⁰ to address the liability for off-label use and patient safety of clofazimine when used to treat TB, and for the drug to become available for MDR and XDR-TB treatment.

Eight years on, the difficulties in accessing clofazimine for DR-TB treatment remain acute⁶¹, with no plan for technology transfer for the finished product formulation to another manufacturer having been announced. Novartis needs to ensure a secure, affordable supply of clofazimine for use in DR-TB treatment, or provide the necessary details for a technology transfer to allow another manufacturer to take over the supply of quality-assured clofazimine. The evaluation of a DR-TB indication for clofazimine will take several years. In the meantime, as recommended by WHO, clofazimine is needed for patients with MDR or XDR-TB that have not been cured with other options.

Number of quality sources

Clofazimine produced by Sandoz India for Novartis is currently the sole quality-assured source of the drug. Although there are additional manufacturers in India and Europe, there has been very little effort to identify a second potential quality-assured source in order to ensure access to clofazimine for DR-TB.

In order to send a clear message to manufacturers that clofazimine is needed, the drug was included in the WHO Prequalification 13th Expression of Interest in August 2015. Clofazimine is also included in the joint GDF/Global Fund Invitation to Manufacturers to submit an Expression of Interest for the evaluation of products by the Expert Review Panel.⁶²

As demand for clofazimine is expected to grow in light of the increased use of shortened regimens, there is a need for alternative quality-assured sources of the drug other than the existing Novartis product, which is not easily available.

Evolution in price

Price is not currently a barrier for patients to access clofazimine, but rather Novartis's restrictive approach to the supply of this drug, which it reserves exclusively for leprosy treatment.

The GDF catalogue lists clofazimine at 100mg and 50mg strengths. The product can be procured for non-leprosy use on a named-patient basis only. With this caveat, it can be procured at a price of US\$1.10 per 100mg capsule and \$0.55- \$0.71 per 50mg capsule through Pharmaworld, a supplier in Switzerland.^{63,64}

Paediatrics

The safety and effectiveness of clofazimine in children has not been established.

While dosages are published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years.

A 50mg soft-gel capsule is currently available, but this formulation makes it impossible to fraction the dose for children.

HIV co-infection

Clofazimine may have a significant drug-drug interaction with some antiretrovirals. No studies have been performed, but clofazimine is a weak inhibitor of the CYP3A4 metabolism pathway and may increase levels of protease inhibitors and etravirine.

Special caution

Clofazimine can affect cardiac conduction (QT prolongation). QT prolongation can infrequently result in a serious (rarely fatal) fast/irregular heartbeat, known as torsades de point. This is an important consideration as several other drugs, such as moxifloxacin, delamanid and bedaquiline have a similar risk and it is unclear if this will be an additive effect.



LINEZOLID (Lzd)

GROUP 5

GENERAL INFORMATION

- Therapeutic Class: Oxazolidinone antibiotic.
- ATC Code: J01XX08.³⁶
- Included in the WHO Guidelines as a Group 5 medicine (agents with unclear efficacy).³⁷
- Linezolid has been included for the first time in the 19th edition of the WHO Model List of Essential Medicines²³ and in the 5th edition of the WHO Model List of Essential Medicines for Children with a tuberculosis indication.³⁸
- Presentations available: 600mg tablet; 100mg/5ml powder for suspension.
- First approved by US FDA: 18 April 2000.⁵⁷
- Approved indication in US: Linezolid is indicated for treatment of susceptible strains of designated microorganisms for nosocomial pneumonia; and complicated and uncomplicated skin and skin structure infections. It is not indicated for the treatment of Gram-negative infections and community-acquired pneumonia.⁶⁵

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Hetero	Macleods	Pfizer	GDF pooled procurement
Quality status	SRA approved	Under evaluation by WHO PQ	SRA approved	GDF Quality Assurance policy
600mg tablet	5.800	5.500	Manufacturer did not agree to publish prices	5.350-5.480
100mg/ml powder for suspension	xx	xx	Manufacturer did not agree to publish prices	xx

SPOTLIGHT ON ACCESS ISSUES

With capreomycin and PAS, linezolid is one of the three medicines which weigh heavily in the overall cost of a DR-TB regimen.

Although linezolid has no official indication for DR-TB treatment, the 2011 WHO programmatic guidelines recommend the use of linezolid as a Group 5 drug³⁷ for patients with MDR or XDR-TB, when there are no other options available. In April 2012, a systematic review outlined the efficacy of linezolid in DR-TB treatment.⁶⁶ Data has also been presented at international conferences, and small case series reports have been published.⁶⁷ The literature review has allowed the WHO Expert Committee to add linezolid to the WHO EML with a DR-TB indication.

Linezolid has a relatively high number of adverse side effects, including myelosuppression, anaemia, and irreversible peripheral and optical neuropathies. Nonetheless, linezolid plays a pivotal role in the treatment of patients with XDR-TB.⁶⁸ The use of linezolid is expected to grow with the increased use of new drugs bedaquiline and delamanid, due to the importance of not adding a single (new) drug to a failing regimen, and due to linezolid's lack of a QT effect.

Number of quality sources

Currently two manufacturers – Pfizer and Hetero – are approved by a stringent regulatory authority.

In addition, Macleods and one further source are under WHO PQ evaluation.

Teva had a 'First To File' status for linezolid with the US FDA – which provides 180 days of generic drug exclusivity on the market before

other generic companies can enter the market with their own products – and subsequently launched their generic linezolid on the US market at the end of June 2015, with no plans to supply other markets. A further five manufacturers (Mylan, Glenmark, Amneal, Alkem and Gate Pharma) have tentative approval from the US FDA. The primary patent on linezolid expired at the end of 2014 in most countries, including in the USA.

Nevertheless, due to Teva's 'First to File' status giving them market exclusivity on linezolid for six months, other generic companies will be able to market their own product only from January 2016; Mylan has since launched their generic linezolid.⁶⁹

Apotex Canada is also another source of quality-assured linezolid supplying only the Canadian

market. The availability of additional quality-assured sources for DR-TB patients is required to address the needs of DR-TB programmes for affordable sources of this product.

Linezolid is included in the 13th WHO Prequalification Expression of Interest (since August 2015) with two dosages, 600mg coated tablet and 150mg dispersible tablet.

In case of severe anaemia and severe peripheral neuropathy, patients should be switched from a 600mg to a 300mg dose; there is a need for 600mg scored tablets or 300mg strength tablets.

Evolution in price

Although the primary patent has expired in the US and most other countries, the cost of the drug is extremely high. Patients failing conventional DR-TB treatment but who could have a chance to survive through the use of linezolid are often denied this option due to the prohibitively expensive cost of the drug.

In South Africa, for example, the price of Pfizer-produced linezolid in the private sector is ZAR655 (US\$47) per tablet. With the treatment duration using linezolid lasting on average four to six months, this takes the cost per patient of linezolid alone to around \$10,000 to \$15,000 – to which the cost of other medicines in the regimen needs to be added. Considering the current commitment by the South African Ministry of Health to start 3,000 patients on bedaquiline before the end of 2016, and the need of linezolid as a companion drug to bedaquiline, the high cost of linezolid will remain a limiting factor for scale up.

The availability of more quality-assured generic sources of linezolid and the increase in order volumes have changed matters somewhat. Although the price has decreased by 22% since 2013, the price still remains high, with the current lowest price at \$5.35 per tablet.

Patents

The basic patent claiming linezolid was filed by Upjohn Company* in the US in 1993 and expired in 2014⁷⁰ in the US and China. In South Africa, the key patents on linezolid⁷¹ also expired in 2014. Upjohn Company also filed patents in the US on a crystalline form II which will expire in the US by 2021.⁷² The crystalline form patent has been rejected in Brazil, has lapsed in South Africa, and has ceased in China, but it remains valid in India until 2021.⁷³

There is also a tablet formulation patent filed in the US in 2001.⁷⁴ This tablet formulation patent has been granted in India and China⁷⁵, and will remain valid until 2021. However, the same patent on the tablet formulation has lapsed in South Africa due to non payment of fees⁷⁶, has lapsed and been withdrawn from the European Patent Office⁷⁷, and has lapsed in Brazil due to non payment of fees.⁷⁸

In India, the basic compound patent could not be filed in 1993 since India's patent law did not allow for pharmaceutical product patenting at the time. However, as mentioned above, the patent applications on the crystalline form II and the tablet formulation, which have been rejected, lapsed, withdrawn or ceased in other countries, have been granted in India and will only expire in 2021.⁷⁹ However, none of these block generic competition. Several Indian generic companies produce the API and have been marketing generic versions of linezolid for several years.

More recently, a patent on a process which is more economical for the preparation of linezolid has led to a legal dispute among generic companies. Symed Labs – a subsidiary of Hetero Drugs – has enforced its API process-related patents (IN213062 and IN213063) against Glenmark, Alkem and other companies, and successfully obtained injunctions against them. This patent dispute was finally

settled when Alkem and Glenmark committed to not infringe the patented process in the production of linezolid. Currently Hetero Drugs therefore holds considerable control over the most efficient process of API production.⁸⁰

As of November 2015, the Medicines Patent Pool (MPP) has a mandate to negotiate voluntary licences for TB drugs. There is no indication yet whether Pfizer or other companies that own secondary patents will provide broad, public health-friendly voluntary licences to the MPP that take into account all remaining secondary patents for linezolid which may block some generic producers – especially those in China and India – in producing and entering into a particular market.

Paediatrics

Pharmacokinetic studies have been completed in children from birth, and dosages are approved by the US FDA exclusively for infections with gram-positive bacteria resistant to other antibiotics.

A paediatric formulation exists as a solution for suspension, produced by Pfizer. The reconstituted product can be stored at room temperature. Although linezolid 150mg dispersible tablet has been introduced in the Expression of Interest of the WHO PQ, no dossier has been submitted yet.

There is a need for further safety and efficacy data on the use of linezolid for extended periods in children with DR-TB.

HIV co-infection

No antiretroviral interaction studies have been performed but interactions are unlikely. There may, however, be an increased risk of myelosuppression and mitochondrial toxicities with long-term use in combination with certain antiretrovirals (zidovudine, stavudine, didanosine). Further studies are required to confirm this.

* In 1995, Upjohn merged with PharmaciaAB, to form Pharmacia & Upjohn. After subsequent restructuring, today the remainder of Upjohn is owned by Pfizer.



BEDAQUILINE (Bdq)

NEW DRUG/GROUP 5

GENERAL INFORMATION

- Therapeutic Class: diarylquinoline (first-in-class) with bactericidal and sterilising activity against *Mycobacterium tuberculosis* or other mycobacterial species.⁸¹
- ATC Code: J04AK05.⁸²
- WHO issued interim guidelines on the use of bedaquiline to treat MDR-TB in June 2013⁸³; bedaquiline was allocated to Group 5 drugs.
- Bedaquiline has been included for the first time in the 19th edition of the WHO Model List of Essential Medicines.²³
- Presentations available: 100mg tablet.
- First conditionally approved by US FDA: 28 December 2012.⁸⁴
- Approved indication in US: Treatment of multidrug-resistant pulmonary tuberculosis in adults. Bedaquiline is indicated for treatment of pulmonary multidrug-resistant tuberculosis as part of combination therapy only when an effective treatment regimen cannot otherwise be provided.⁸⁵

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Janssen	GDF pooled procurement
Quality status	SRA approved*	GDF Quality Assurance policy
100mg tablet	Tiered pricing based on disease burden and affordability. Please refer to both GDF and/or USAID donation program.	Free of charge (donation)

* Bedaquiline received US FDA accelerated approval on the basis of phase IIb clinical trial data.

SPOTLIGHT ON ACCESS ISSUES

Bedaquiline received conditional approval by the US FDA in late December 2012 based on Phase II clinical trial data. Janssen Pharmaceuticals are required to submit additional clinical data for the drug to receive full FDA approval.⁸⁶

The first compound in the diarylquinoline class, bedaquiline's novel mechanism of action inhibits mycobacterial adenosine 5'-triphosphate (ATP) synthase. The drug is intended as part of combination therapy for DR-TB, and it inhibits both actively replicating and non-replicating wild-type and resistant *M. tuberculosis*.

In placebo-controlled studies of MDR and XDR-TB patients (including those co-infected with HIV), 79% of patients given bedaquiline had negative TB cultures after 24 weeks. Culture conversion happened 33% faster in patients taking bedaquiline as compared to the standard WHO-recommended MDR-TB regimen.^{87,83}

There are concerns around safety however. During drug trials, 10 out of 79 patients in the bedaquiline group died, compared to 2 out of 81 patients

in the standard treatment group. Although many of these deaths are attributed to TB itself, the difference is significant and a source of concern, and needs careful future monitoring as the use of bedaquiline increases. Assessing these concerns should form part of phase III trials.

WHO issued interim guidelines on the use of bedaquiline to treat MDR-TB in June 2013.⁸³ The scale up of programmatic use of bedaquiline has been slow but is increasing, with just over 2,300 patients on bedaquiline as part of programmatic use as of February 2016.¹⁵

At this time there is no evidence on the safety and efficacy of combining bedaquiline with delamanid, and currently there is no recommendation regarding their combination. Drug-drug interaction studies are due to commence in early 2016 to look at the cardiac safety of combining these two drugs with QT prolongation potential.⁸⁸

Number of quality sources

Janssen is currently responsible for all global manufacturing of bedaquiline.

When greater numbers of patients are reached worldwide in the future, Janssen may look into engaging with other global partners for production and/or marketing.

Bedaquiline has received approvals in 9 out of the 27 high MDR-TB burden countries – where 60% of total patients from the high burden countries live – Russia, India, South Africa, Philippines, Peru, South Korea, Turkmenistan, and Armenia, and has ongoing submissions in 9 of 27 high MDR-TB burden countries (covering a further 20% of total patients from high burden countries). Bedaquiline has recently been registered by the Indian Central Drugs Standard Control Organisation for use in the treatment of multidrug-resistant TB under the strict supervision of the Revised National Tuberculosis Control Program. Sale or supply of bedaquiline in the private sector is not allowed.

The file to register bedaquiline has been rejected in Kyrgyzstan due to a lack of phase III clinical studies. In addition, Janssen entered into a licensing agreement with Pharmstandard to

register and commercialise bedaquiline in the Commonwealth of Independent States as well as in Georgia, Turkmenistan and Ukraine. By the end of 2015 Janssen announced it was phasing out its compassionate use programmes, which had been the major access channel of bedaquiline until its donation came into effect.

Prices

Janssen officially announced a donation programme for bedaquiline on 11 December 2014⁸⁹, where over the next four years, they will donate 30,000 treatment courses of bedaquiline. From 1 April 2015, bedaquiline ordered through the Global Drug Facility is free if procured for countries eligible for the Janssen donation (eligible countries are Global Fund-eligible countries for TB grants), with South Africa being excluded from the donation.

Janssen communicated for the purposes of this report that it will be implementing a three-tiered pricing 'framework', in an attempt 'to balance a country's ability to pay with the burden of disease' for countries that are not eligible for Global Fund grants.⁹⁰ Countries will be classified into three groups, which initial communication with the company suggests will be labelled 'high-income', 'upper middle-income', and 'least-developed/resource-limited'. For a six-month treatment course, a country in the high-income bracket would pay US\$30,000, a country in the upper middle-income bracket would pay \$3,000, and a country in the least-developed/resource-limited bracket would pay \$900. Janssen points to the fact that its proposed pricing for the middle and lower pricing tiers is aligned with a WHO-sponsored cost effectiveness assessment of bedaquiline.⁹¹

Janssen have indicated that countries will be classified in the 'framework' both according to World Bank gross national income per capita definitions and according to disease burden as per the WHO's MDR- and XDR-TB 2010 Global Report on Surveillance and Response. However, the company was unwilling to divulge placement of individual countries in the three respective groups until regulatory efforts had concluded (and, where applicable, 'following completion of reimbursement processes'). It remains to be seen what pricing will be offered to countries like China which is simultaneously a high-burden TB country and in the upper middle-income bracket.

Patents

Bedaquiline is a newly approved drug and UNITAID has published a patent

landscape report of its patent status in major developing countries.⁹²

The base compound patent on bedaquiline has been granted in India, China and South Africa, which will expire between 2023-2025.⁹³ The patent application on the base compound remains pending in Brazil.⁹⁴

The basic patent has also been granted in several countries including Armenia, Azerbaijan, Kazakhstan, Russia, Tajikistan, Ukraine and a number of African Intellectual Property Organisation (ARIPO) and Organisation Africaine de la Propriété Intellectuelle (OAPI) countries.⁹⁴

In India, the patent office has granted the compound patent on bedaquiline – IN236811 – to Janssen which will expire in 2023. Generic manufacturers are not keen to develop the drug unless they are provided a licence to market and supply developing countries. Janssen has filed several other types of evergreening patent applications for bedaquiline that, if granted, would further extend Janssen's monopoly and restrict the timely entry of affordable generic versions in India and many developing countries. The patent on the use of bedaquiline in treating DR-TB (6315/DELNP/2006) has been granted (IN264718) and this patent expires only in May 2025.⁹⁵ This patent has also been granted in South Africa, but remains pending in China and Brazil.⁹⁴

The Indian application on the salt form (1220/MUMNP/2009) was opposed in March 2013 by the Network of Maharashtra People Living with HIV (NMP+), and the decision is awaited.⁹⁶ This patent remains pending in China and Brazil, but has been granted in South Africa.⁹⁴

Another patent application covering the process of preparation of bedaquiline, including its API, is pending, and if granted will expire in 2026.⁹⁷ This patent has also been granted in South Africa and China, but remains pending in Brazil.⁹⁴

It is also important to note that bedaquiline is included in patents for tuberculosis combination therapies. These patents, such as WO2010026526, can potentially block the development of new treatment regimens.⁹⁸ This patent is pending in several countries and if granted it would not lapse before 2029.

Given the patent barriers on bedaquiline both as a standalone treatment and as a part of combination therapies, a proactive strategy will be needed to mitigate access challenges.

Secondary and follow-on patents are a typical problem in the area of pharmaceuticals and such patents often extend monopolies even after the expiry

of compound patents. This problem can partially be addressed by applying strict patentability criteria and by proactively challenging secondary patents. In India and in other countries where such strategies can be employed, pre-grant oppositions of patent applications by third parties on secondary patents for bedaquiline will therefore be an important strategy to avoid patent term extensions beyond the expiry of the basic patent in 2023.

In addition, some governments – and particularly India, where the product patent blocks the manufacture of generics even for export to countries where there is no applicable patent – will have to decide whether to employ compulsory licensing to enable the production, use and export of more affordable generic versions.

As of November 2015, the Medicines Patent Pool (MPP) has been given a mandate to negotiate voluntary licences for TB drugs.⁹⁹ There is no indication yet whether Janssen will negotiate a voluntary licence with the MPP that will include a broad geographic scope that includes all low- and middle-income countries.

Paediatrics

The safety and effectiveness of bedaquiline in children has not been established.

There is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data) into the use of this drug in younger populations, in particular in children aged under five years. Paediatric studies are planned as part of the paediatric development plan required for the company to complete the regulatory approval process.^{100,101}

There is no paediatric formulation currently available.

HIV co-infection

Early research shows that efavirenz interacts with bedaquiline by reducing its blood concentration, while lopinavir/ritonavir slightly increases the concentration of the drug.

More detailed studies are required.

Special caution

Bedaquiline can affect cardiac conduction (QT prolongation). QT prolongation can infrequently result in a serious (rarely fatal) fast/irregular heartbeat, known as torsades de point. This is an important consideration as several other drugs (such as moxifloxacin and delamanid) and repurposed TB drugs (clofazimine) have a similar risk and it is unclear if this will be an additive effect.



DELAMANID (Dlm)

NEW DRUG/GROUP 5

GENERAL INFORMATION

- Therapeutic Class: nitroimidazole (Nitro-dihydro-imidazo-oxazole derivative).
- ATC Code: J04AK06.⁸²
- WHO issued interim guidelines on the use of delamanid to treat MDR-TB in October 2014. Delamanid was allocated to Group 5 drugs.¹⁰²
- Delamanid was included for the first time in the 19th edition of the WHO Model List of Essential Medicines.²³
- Presentations available: 50mg film coated tablets.
- Approved in April 2014 by the European Medicines Agency (EMA).³²
- Approved indication in EMA: "as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability."³²

PRICE (IN US\$) AND QUALITY INFORMATION

Price of the lowest unit (i.e. the price of one tablet, capsule or vial)

	Otsuka	GDF pooled procurement
Quality status	SRA approved*	GDF Quality Assurance policy
50mg film coated tablet	Manufacturer has not made pricing strategy public for non Global Fund-eligible countries	2.530

* Delamanid received EMA conditional approval on the basis of phase IIb clinical trial data.

SPOTLIGHT ON ACCESS ISSUES

Delamanid received approval from the European Medicines Agency (EMA) and Japan's Pharmaceuticals Medical Devices Agency (PMDA) in 2014. Delamanid, previously OPC-67863, is a drug of the dihydro-nitroimidazole class and is thought to primarily inhibit synthesis of methoxy-mycolic and keto-mycolic acid, components of the mycobacterial cell wall.

Clinical trial data come from three related Phase IIb studies on the same cohort of MDR-TB patients (Trial 204, Trial 208 and Observational Study 116). These studies showed promising results amongst patients who received 6-8 months of treatment with delamanid, compared to those who received 0-2 months of delamanid, with significantly higher proportion

of favourable outcomes (cure or treatment completed) (75.5% versus 55%) and lower mortality (1% versus 8.3%).

The Phase III trial to assess efficacy against MDR-TB using six months of delamanid added to a WHO-recommended Optimal Background Regimen has recently completed recruitment and results are expected late 2017/early 2018.

WHO issued interim guidelines on the use of delamanid to treat MDR-TB in November 2014. The scale up of the use of delamanid has been slow, with just 180 patients on delamanid outside of clinical trials as of February 2016. The majority of patients who have accessed delamanid have done so through compassionate use programmes.

In February 2016, Otsuka and the GDF announced a price of \$1,700 per treatment course, available to Global Fund-eligible countries through the GDF.³¹ However, with delamanid currently registered in just Japan, South Korea and the European Union, programmatic access in the medium term will remain extremely difficult, while in the short term, most countries will have to issue import waivers.

At this time there is no evidence on the safety and efficacy of combining delamanid with bedaquiline, and there is no recommendation regarding their combination. Drug-drug interaction studies are due to commence in early 2016 to look at the cardiac safety of combining these two drugs with QT prolongation potential.¹⁰³

Prices

The GDF price for Global Fund-eligible countries is \$1,700 per treatment course.³¹ Given that delamanid is just one drug combined with multiple other drugs needed to form a DR-TB regimen, this price is prohibitively expensive for most high-burden countries. The manufacturer has not disclosed the pricing strategy for non Global Fund-eligible countries.

Number of quality sources

Delamanid has received approval only from the EMA, Japan and South Korea. Registration has been submitted in China and Hong Kong.

Patents

The originator company Otsuka has applied multiple patents upon delamanid.

India - a key producer of TB drugs - has granted the compound patent on delamanid (IN250365) to Otsuka Pharmaceutical Ltd, which is set to expire in 2023. By granting the salt form patent (9790/DELNP/2009) of the drug (an obvious form), the patent office has already extended the monopoly an additional three years, from 2023 to 2026. Another application (1255/KOLNP/2008) on its use in combination with other drugs has been also granted.

Further, Otsuka, which holds multiple Indian patents (DEL compound IN250365, DEL salt form IN253642 and DEL combination IN268015) for this drug, has also not exerted itself to work the patent in India by filing for registration, doing necessary local trials or making the drug available to the national TB programme, even though over three years have lapsed since the grant of the patents.

The working statement (Form 27) related to the patents on the drug, as submitted to the Indian patent office, reveals a startling fact - that the patented invention is not being worked in India. The working statement also shows that neither is it being imported from any other country, nor there are any applicable licences or sub-licences on the invention.

The patent on the base compound of delamanid has also been granted in China, South Africa and the US, and will expire between 2023-2025.⁹⁴ The patent application remains pending in Brazil.⁹⁴ In addition, there is one patent on the composition of delamanid and its derivative forms¹⁰⁴, and another patent on the combination of delamanid and other compounds¹⁰⁵, have been granted in India, China and South Africa, and remain pending in Brazil.⁶⁰ These patents will remain valid until 2026.⁹⁴

A number of other secondary patents on delamanid may also add to the obstacles in introducing generic products into the market. In particular, two patents covering the process of producing delamanid intermediates have been granted in India and China, and will remain valid until 2023-2025.^{106,107} A separate patent on the process of preparation of delamanid has also been granted in India and China, and will expire in 2025.¹⁰⁸ In China, an additional patent on delamanid intermediate has also been granted and will expire in 2031.¹⁰⁹

As of November 2015, the Medicines Patent Pool (MPP) has been given with a mandate to negotiate voluntary licences for TB drugs.

There is no indication yet whether Otsuka will negotiate a voluntary licence with the MPP that will include a broad geographic scope that includes all low- and middle-income countries.

Paediatrics

The safety and effectiveness of delamanid in children has not been established.

Paediatric studies are currently underway. Bioequivalence studies have been completed. Patient cohorts have commenced enrolment with data submitted for 6 to 15 years old age group, commencing enrolment for the 3 to 5 years old cohort and 0 to 3 years old groups.

There is a paediatric formulation under development.

HIV co-infection

Early research shows delamanid does not have a significant effect on concentrations of tenofovir, lopinavir-ritonavir, or efavirenz. Lopinavir plus ritonavir however, was associated with a 20% increase in delamanid exposure and a 30% increase in delamanid's metabolite DM-6705.¹¹⁰

More detailed studies are required.

Special caution

Delamanid can affect cardiac conduction (QT prolongation). QT prolongation can infrequently result in a serious (rarely fatal) fast/irregular heartbeat, known as torsades de point. This is an important consideration as several other drugs (such as moxifloxacin and bedaquiline) and repurposed TB drugs (clofazimine) have a similar risk and it is unclear if this will be an additive effect.

ANNEX 1: SUMMARY TABLE OF PRICES PROVIDED BY PHARMACEUTICAL COMPANIES

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

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

Drug	GDF pooled procurement	Companies					
AMIKACIN	GDF	Cadila	Cipla	Pharmatex	Vianex		
500mg/2ml solution for injection	0.678-0.805	0.980	1.600	0.678	2.500		
KANAMYCIN		Macleods	Meiji	Panpharma			
1g powder for injection	1.000-1.721	1.000	xx	Manufacturer did not agree to publish prices			
1g/4ml solution for injection	2.560	xx	Manufacturer did not agree to publish prices	xx			
CAPREOMYCIN		Akorn	Aspen	Hisun	Macleods	Vianex	
1g powder for injection	3.800-4.700	8.000	8.100	Manufacturer did not agree to publish prices	4.150	6.000	
MOXIFLOXACIN		Cipla	Hetero	Macleods	Microlabs	Sunpharma	
400mg tablet	0.437-0.540	0.600	0.660	0.580	Manufacturer did not agree to publish prices	0.510	
LEVOFLOXACIN		Apotex*	Cipla	Hetero	Labatec	Macleods	Microlabs
250mg tablet	0.033-0.055	0.090	0.061	0.059	1.538	0.043	0.057
500mg tablet	0.059-0.097	0.130	0.110	0.105	2.315	0.078	0.092
750mg tablet	0.100	0.150	xx	0.240	xx	0.128	xx
ETHIONAMIDE		Macleods	Cipla	Lupin	Macleods	Microlabs	
125mg tablet	xx	0.112	xx	xx	xx	xx	
250mg tablet	0.062-0.080	xx	0.098	Manufacturer did not agree to publish prices	0.066	0.082	
PROTHIONAMIDE		Fatol	Lupin	Microlabs	Olainfarm		
250mg tablet	0.130-0.178	Manufacturer did not agree to publish prices	Manufacturer did not agree to publish prices	0.120	0.100		
CYCLOSERINE		Cipla	Dong-A	Macleods	Microlabs	Strides	
250mg cap	0.187-0.330	Price was not available at time of data collection	0.216	0.390	Manufacturer did not agree to publish prices	0.600	
TERIZIDONE		Fatol	Macleods				
250mg capsule	1.588-1.666	Manufacturer did not agree to publish prices	0.850				
PAS		Jacobus					
4g sachet	1.333	1.500					
PAS-SODIUM		Macleods	Olainfarm				
60% w/w granules – 9.2g sachet	1.690	1.690	xx				
60% w/w granules – 100g jar	18.360	18.360	xx				
Powder for oral solution – 5.52g sachet	1.370	xx	1.400				
CLOFAZIMINE		Novartis					
50mg soft-gel capsule	0.547-0.713	Manufacturer did not agree to publish prices					
100mg soft-gel capsule	1.095-1.267	Manufacturer did not agree to publish prices					
LINEZOLID		Hetero	Macleods	Pfizer			
600mg tablet	5.350-5.480	5.800	5.500	Manufacturer has not made pricing strategy public			
100mg/ml powder for suspension	xx	xx	xx	Manufacturer has not made pricing strategy public			
BEDAQUILINE		Janssen					
100mg tablet	0.00 (donation)	Tiered pricing based on disease burden and affordability. Please refer to both GDF and/or USAID donation program					
DELAMANID		Otsuka					
50mg film coated tab	2.530	Manufacturer has not made pricing strategy public for non Global Fund-eligible countries					

* Incoterm CIF

ANNEX 2: CONDITIONS OF OFFER, AS QUOTED BY COMPANIES

Definitions of eligibility vary from company to company. The conditions detailed in the table below are those quoted by companies.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
AKORN	Price is eligible outside US and Canada only	No restriction	Min. purchase: one batch	Ex-works
APOTEX	No restriction	No restriction		CIF by air to airport of destination
ASPEN	South Africa only	No restriction		Ex-works
CADILA	All countries except European countries & USA	No restriction	Price is valid until November 2016	Ex-works
CIPLA	Generic accessible countries	Public sector		Ex-works
DONG-A				Ex-works
FATOL	No restriction	No restriction		Ex-works
HETERO	No restriction	No restriction		Ex-works
JACOBUS	No restriction	No restriction		Ex-works
JANSSEN	All countries	In low- and middle-income countries, bedaquiline is made available through the Global Drug Facility. Alternatively, for selected middle- and high-income countries bedaquiline is also supplied through the local Janssen affiliate directly to the MoH/NTP (or designated purchasing entities).	As of 1st April 2015, USAID and Janssen have jointly announced a four-year bedaquiline donation program. For further details on eligibility please refer to http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp	Delivery of goods is done in a majority of cases via the Global Drug Facility. Please refer directly to the GDF for full information.
LABATEC				
LUPIN	All countries where GDF, MSF, UNDP, PAHO or Damien are supplying TB medicines to MoH and/or specific projects.	All institutional buyers, including GDF, MSF, PAHO, UNDP and Damien.		Ex-works
MACLEODS	Prices are subject to volumes and registrations. Macleods will not ship to countries where products are under patent. Macleods will not ship to countries where products are not registered, without a registration waiver.	Prices are subject to volumes. Macleods has no restrictions in selling products to any customer.		Ex-works
MICROLABS	No restriction	No restriction		Ex-works
OLAINFARM	No restriction	No restriction		Ex-works
OTSUKA	No price communicated	No restriction		Ex-works
PANPHARMA				
PHARMATEX	No restriction	No restriction		Ex-works
SUNPHARMA	No restrictions as long as goods are imported against an import permit or a valid registration in that country.	No restriction		Ex-works
VIANEX	No restriction except USA	No restriction		Ex-works

For more information on incoterms used to describe delivery of goods, please refer to the Glossary.

ANNEX 3: COMPANY CONTACTS

This section reports the contact details of companies that have been contributing with price information to this publication.

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ABBREVIATIONS

- | | | |
|---|--|---|
| ANDA – Abbreviated New Drug Application | GDF – Global Drug Facility | PAS – Para-aminosalicylic acid |
| API – Active pharmaceutical ingredient | GFATM – Global Fund to Fight AIDS, Tuberculosis and Malaria | PIH – Partners In Health |
| API PQ – Active Pharmaceutical Ingredient-Prequalification | GLC – Green Light Committee | PQ – Prequalification |
| CEWG – Consultative Expert Working Group | HIV – Human immunodeficiency virus | R&D – Research and development |
| CIS – Commonwealth of Independent States | IDR – Interactive Research & Development | SRA – Stringent regulatory authority |
| DR-TB – Drug-resistant tuberculosis | IP – Intellectual property | TB – Tuberculosis |
| DS-TB – Drug-sensitive tuberculosis | LIC – Low-income countries | TDR-TB – Totally drug-resistant tuberculosis |
| EMA – European Medicines Agency | MDR-TB – Multidrug-resistant tuberculosis | TRIPS – (Agreement on) Trade-Related Aspects of Intellectual Property Rights |
| EML – Essential Medicines List | MCC – Medicines Control Council (South Africa) | USAID – US Agency for International Development |
| EOI – WHO Prequalification Expression of Interest | MIC – Middle-income countries | US FDA – US Food and Drug Administration |
| ERP – Expert Review Panel | MRC – Medical Research Council (UK) | <i>w/w</i> – weight for weight |
| EU – European Union | MSF – Médecins Sans Frontières | WHO – World Health Organization |
| FDC – Fixed-dose combination | NMRA – National Medicine Regulatory Authority | WHO PQ – World Health Organization Prequalification Programme |
| GLI – Global Laboratory Initiative | NGO – Non-governmental organisation | XDR-TB – Extensively drug-resistant tuberculosis |

Abbreviated New Drug Application (ANDA)

An Abbreviated New Drug Application (ANDA) contains data that, when submitted to the US FDA, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called “abbreviated” because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e. performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low-cost alternative in the US.

Bangladesh trial/regimen

A non-randomised observational study in Bangladesh which looked at a nine-month combination of existing TB drugs for the treatment of MDR-TB. The study regimen included ethambutol, pyrazinamide, gatifloxacin and clofazimine throughout, supplemented by kanamycin, prothionamide and high-dose isoniazid in the first four months.

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form.

CIF: Cost, Insurance and Freight (named port of destination)

A commercial term (incoterm 2010), meaning that the seller must pay the costs and freight to bring the goods to the port of destination. Risk is transferred to the buyer once the goods are loaded on the vessel. Insurance for the goods is included and paid by the seller; only maritime transports are covered.

CIS: Commonwealth of Independent States

The Commonwealth of Independent States is a regional organisation formed during the breakup of the Soviet Union, whose participating countries are some former Soviet Republics.

Clinical trials

Sets of tests in medical research and drug development that generate safety and efficacy data (including information about adverse drug reactions and

adverse effects of other treatments) for health interventions (e.g., drugs, diagnostics, devices, therapy protocols).

Compassionate Use

The terms “compassionate use,” “expanded access” or “special access” programmes have essentially the same meaning. They refer to programmes that are intended to provide potentially lifesaving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial. It refers to programmes that make medicinal products available either on a named-patient basis or to cohorts of patients. Compassionate use needs to be framed within national legislation that establishes under what conditions the drug is made available. Refer to Annex 5 (*Use of experimental drugs outside of clinical trials “compassionate use”*) of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008.

Culture

Bacterial culture is a laboratory method to multiply bacteria in order to assess their presence or not in a patient’s sample. This is done by letting the bacteria grow in predetermined culture media under controlled laboratory conditions, outside the natural environment where they usually grow (e.g. for TB, the human body).

Drug resistance

When a drug used to treat tuberculosis is in fact ineffective against a strain of *M. tuberculosis*, the bacteria is said to be resistant to the drug (as opposed to drug-susceptible or drug-sensitive).

Drug-susceptible/drug-sensitive TB

Bacteria are said to be sensitive to a drug when the drugs are effective in killing or stopping the multiplication of bacteria in the body and can therefore clear the infection. The strains of TB which are sensitive to all first-line drugs are called drug-susceptible.

Ex-works

A commercial term (incoterm 2010) meaning that the seller delivers when the goods are placed at the disposal of the buyer at the seller’s premises or another named place (i.e. works, factory, warehouse etc.), not cleared for export and not loaded on any collecting vehicle.

Expert Review Panel (ERP)

An independent technical body composed of external technical experts, hosted by the WHO Department of Essential Medicines and Pharmaceutical Policies. Their purpose is to review the potential risks and benefits associated with the use of antiretroviral, anti-TB and antimalarial products which are not yet WHO-prequalified or authorised by a stringent regulatory authority. The ERP makes recommendations to the Global Fund and the Global Drug Facility on whether procurement of such products can be authorised. The recommendation is valid for a period of no more than 12 months or until the product is either WHO-prequalified or SRA-authorized. (<http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/>).

Extensively drug-resistant TB

see XDR-TB

Extra-pulmonary TB

Form of TB where *M. tuberculosis* infects parts of the body other than the lungs. This occurs most commonly in the lymph nodes, bones, central nervous system, cardiovascular and gastrointestinal systems.

First-line drugs

The drugs used as the first resort to treat a disease. In the case of TB, the following four drugs are usually chosen: isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z). These drugs are highly effective in drug-susceptible TB and patients usually tolerate them well. Streptomycin (S) injectable is used in first-line treatment of TB meningitis.

Global Drug Facility (GDF)

A mechanism hosted by UNOPS to expand access to, and availability of, quality-assured anti-TB drugs and diagnostics through pooled procurement. Products procured comply with the GDF’s Quality Assurance policy, which deems eligible for GDF procurement all products that are included on the WHO List of Prequalified Medicinal Products, that are approved by a stringent regulatory authority, or that are temporarily approved by the Expert Review Panel.

Global Fund

The Global Fund to Fight AIDS, Tuberculosis and Malaria is an international financing institution that invests in 150 countries to support large-scale prevention, treatment and care programs against the three diseases.

Continued overleaf ❖❖❖

Green Light Committee (GLC)

The GLC Initiative was created in 2001 to help countries gain access to quality-assured second-line anti-TB drugs so they could provide treatment for people with multidrug-resistant tuberculosis in line with the WHO guidelines, the latest scientific evidence and country experiences. The Initiative originally consisted of a secretariat, the GLC (an expert review and WHO advisory body) and the Global Drug Facility (the drug procurement arm of the Initiative). As of 2011, GLC approval is no longer needed to procure quality-assured second-line TB drugs through GDF. GLC was restructured in June 2011 into a Global GLC (gGLC) and regional GLC (rGLC) to focus on monitoring and technical assistance to National TB programmes in countries and WHO.

Microscopy

Microscopy is currently the most commonly used technique to diagnose TB. Two to three sputum samples are taken from the patient and the sample is stained and later read under the microscope. If TB bacilli are present, they occur in the form of small red rods, while the rest of the sample is blue.

Multidrug-resistant TB (MDR-TB)

Patients infected with strains of TB that are resistant to (at least) the two most powerful first-line antibiotics used to treat TB, namely rifampicin and isoniazid, are said to have multidrug-resistant TB, or MDR-TB.

Mycobacteria

Types of bacteria, of the genus *Mycobacterium*, that cause diseases such as TB and leprosy.

M. Tuberculosis

Mycobacterium tuberculosis
A pathogenic bacterial species of the genus *Mycobacterium* and the causative agent of most cases of TB. First discovered in 1882 by Robert Koch.

New Drug Application (NDA)

When the sponsor of a new drug believes that enough evidence on the drug's safety and efficacy has been obtained to meet US FDA requirements for marketing approval, the sponsor submits to US FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States.

Pharmacokinetic (PK)

Branch of pharmacology that studies the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body (e.g. by metabolic enzymes) and the effects and routes of excretion of the metabolites of the drug.

Pharmacovigilance

The science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems.

Pharmacodynamic (PD)

Branch of pharmacology that studies the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

Point-of-Care testing (POC)

Testing at the point-of-care means that diagnosis is carried out as close as possible to the site of patient care. The driving notion behind point-of-care testing is having a test as convenient to the patient as possible and giving immediate results that can lead to prompt initiation of treatment.

Pulmonary TB

Form of TB where *M. tuberculosis* bacteria are infecting the lungs.

QT Interval

In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. This represents the total duration of electrical activity of the ventricles. A prolonged QT interval is a biomarker of life-threatening ventricular tachyarrhythmias - including torsades de pointes.

Second-line drugs

Second-line drugs are used when first-line drugs are no longer effective in curing a patient. Second-line TB drugs are less effective and have many more side effects than first-line TB drugs.

Staircase pricing

Global Drug Facility prices occasionally depend on volume, with lower prices per unit if larger quantities are ordered. The GDF refers to this pricing structure as 'staircase pricing'.

Stringent regulatory authority (SRA)

Is a regulatory authority which "is (a) a member of the International

Conference of Harmonization (ICH); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and WHO; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein." Please consult <http://www.ich.org>.

TB Alliance

The TB Alliance is a not-for-profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB patients currently on such therapies, and improve treatment of latent infection. The TB Alliance is committed to ensuring that approved new drug regimens are affordable, widely adopted and available to those who need them.

Tentative FDA approval

Awarded by the US FDA to a drug product that has met all required quality, safety and efficacy standards, but is not eligible for marketing in the US because of existing patent protection. Tentative approval does make the product eligible for purchase outside the US under the US President's Emergency Plan for AIDS Relief (PEPFAR) programme.

Totally drug-resistant (see XDR-TB).

The term "totally drug-resistant TB" was used in 2011 for a group of patients in India presenting resistance to all drugs that they were tested for. The term, while widely used by the media, is not recognised by WHO, which defines those cases as extensively drug-resistant tuberculosis (XDR-TB).

WHO Prequalification (PQ) Programme

The Prequalification Programme, set up in 2001, is a service provided by WHO to make priority medicines available for HIV/AIDS, malaria, tuberculosis and reproductive health that meet unified standards of quality, safety and efficacy. Please consult <http://apps.who.int/prequal/>

XDR-TB (Extensively drug-resistant TB)

Patients, who have MDR-TB and also show resistance to second-line drugs, including at least one from the class known as fluoroquinolones and one of the injectable drugs, are described as having extensively drug-resistant TB or XDR-TB.

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