



DR-TB DRUGS UNDER THE MICROSCOPE

SOURCES AND PRICES FOR DRUG-RESISTANT
TUBERCULOSIS MEDICINES

3rd Edition – October 2013



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The Union, in partnership with experts from sub-Saharan African countries, has produced for NTPs a desk-guide of child TB management for health workers aimed at the district or more peripheral level of care. Available from: <http://bit.ly/1ekSfLI>



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DR-TB DRUGS UNDER THE MICROSCOPE

This report – now in its third edition – analyses the sources and prices of medicines used to treat drug-resistant tuberculosis (DR-TB), examines the key factors that shape the access environment for DR-TB medicines, reviews the research and development landscape for DR-TB treatment regimens, and makes recommendations for the way forward to reach more people and improve treatment outcomes.

MSF clinics and The Union TB experts are recording alarming rates of people with drug-resistant forms of TB, not only among patients for whom first-line treatment has failed, but also in patients newly diagnosed with TB – a clear sign that DR-TB is being transmitted from person to person in the communities in which we work.

Treatment regimens for drug-resistant forms of the disease, which are more difficult to diagnose and treat than drug-sensitive (DS) TB, are notoriously lengthy, toxic, expensive and burdensome to patients. DR-TB patients must endure about two years of treatment with excruciating side effects, including psychosis, deafness and constant nausea, with painful daily injections for up to eight months. Those who make it through the treatment for multidrug-resistant TB (MDR-TB) only have about a 50% chance of being cured; for extensively drug-resistant (XDR) strains, it's just 13%.^{1,2} Meanwhile the current recommended treatment course for MDR-TB costs at least \$3,000 per patient today, compared to just \$22 for drug-sensitive TB treatment.

The utter inadequacy and high costs of today's current recommended DR-TB treatment regimens contribute directly to abysmally low treatment coverage, which in turn allows drug-resistant forms of the disease to spread rapidly. Inadequately treated patients, poor treatment adherence due to intolerable side effects, poor efficacy and the use of low quality TB medicines are also major contributing factors to the unchecked spread of DR-TB strains. DR-TB represents a serious threat to public health, burdening families and communities with high rates

of unnecessary death and sickness, and saddling treatment programmes with much higher costs.³

Although far from ideal, today's current recommended regimens represent one of the few lifelines currently available to people living with DR-TB. Until improved treatment options are widely available, continued use and scale up of the existing treatment regimens must remain a critical component of any strategy to control the DR-TB epidemic.

Today, we're closer than ever to having more tolerable, all-oral, short-course regimens that, if made widely accessible, could fundamentally transform DR-TB treatment. At the end of 2012, the first new TB drug in 50 years received accelerated approval for use in treating MDR-TB, and a second new drug is currently under review. Many questions remain unanswered about how these new drugs should be incorporated into optimal treatment regimens. A historic opportunity could be squandered amid a lack of collaboration and transparency that is critical to evaluating new multi-drug treatment regimens. Furthermore, meaningful treatment scale up will only occur if these new regimens are made available at prices that are substantially lower than today's prohibitively expensive options.

In addition, there is growing evidence that repurposed drugs – drugs with indications for diseases other than TB – can significantly improve patient outcomes, particularly for XDR-TB. Unfortunately, these drugs are not yet readily accessible either for further research or to treat patients,

and there are many barriers to wider use, including cost, regulatory issues and a lack of incentives for industry to promote access.

Looking further ahead, it is important that the drug pipeline for TB has a range of new candidates in each phase of clinical development, to ensure clinicians can stay ahead of new resistance patterns.

Some of these gaps and barriers may take years to resolve, but in the meantime, governments can and should increase rapid screening and diagnosis of DR-TB, increase access to today's treatments, and take concrete steps to ensure that new DR-TB drugs are approved, affordable, and available.

Global health actors, including the Global Fund to fight AIDS, Tuberculosis and Malaria and the Global Drug Facility, should act now to mobilise funding, consolidate demand, and ensure a sustainable supply of new and existing effective DR-TB drugs. The world has waited half a century for newer and more effective TB and DR-TB treatments. Now that hope is on the horizon, concerted efforts are needed on all fronts to avoid any further delay in relieving unnecessary pain and suffering for patients and their families, and in permanently turning the tide against DR-TB.

A GROWING HEALTH CRISIS: TEN FACTS ABOUT DRUG-RESISTANT TUBERCULOSIS

- Although tuberculosis is a preventable and curable disease, it ranks as the second biggest infectious disease killer behind HIV, killing nearly 1.4 million people each year.⁴
- Drug-resistant tuberculosis is increasingly recognised as a public health emergency across the globe, even as the true scope of the problem remains largely hidden and many people living with DR-TB go undiagnosed and uncounted due to inadequate access to diagnostic services.
- The number of people receiving treatment globally remains shockingly low, in particular for MDR forms of TB: in 2011, just one in five people estimated to have contracted MDR-TB, among notified TB cases, were diagnosed and put on treatment.⁴
- Globally in 2011, there were an estimated 630,000 prevalent cases of MDR-TB.
- India, China, Russia and South Africa carry the burden of almost 60% of the world's cases of MDR-TB.⁴
- The highest proportions of TB patients with MDR-TB are in Eastern Europe and Central Asia, where in some countries 50% of previously treated cases have MDR-TB.⁴
- Extensively drug-resistant (XDR) TB has been identified in 84 countries.⁴
- A growing concern is the number of patients acquiring MDR-TB through primary transmission of drug-resistant strains of the disease, rather than through the evolution of resistance in an on-going infection.⁵ As a consequence, in some countries, for example in Kyrgyzstan and Uzbekistan, upwards of 20% of newly-infected patients have DR-TB.⁴
- Globally, amongst those previously treated for TB, about 20% develop MDR-TB, and about 3.7% of newly-infected TB patients receive an initial diagnosis of MDR-TB.
- According to the Stop TB Partnership's Global Plan to Stop TB for the years 2006 to 2015, 1.3 million MDR-TB cases will need to be treated in the 27 high MDR-TB burden countries between 2010 and 2015, at an estimated total cost of US\$16.2 billion.⁶

ALPHABET SOUP

Drug-sensitive tuberculosis, also called drug-susceptible tuberculosis, is responsive to standard first-line TB drugs and is not the subject of this report.

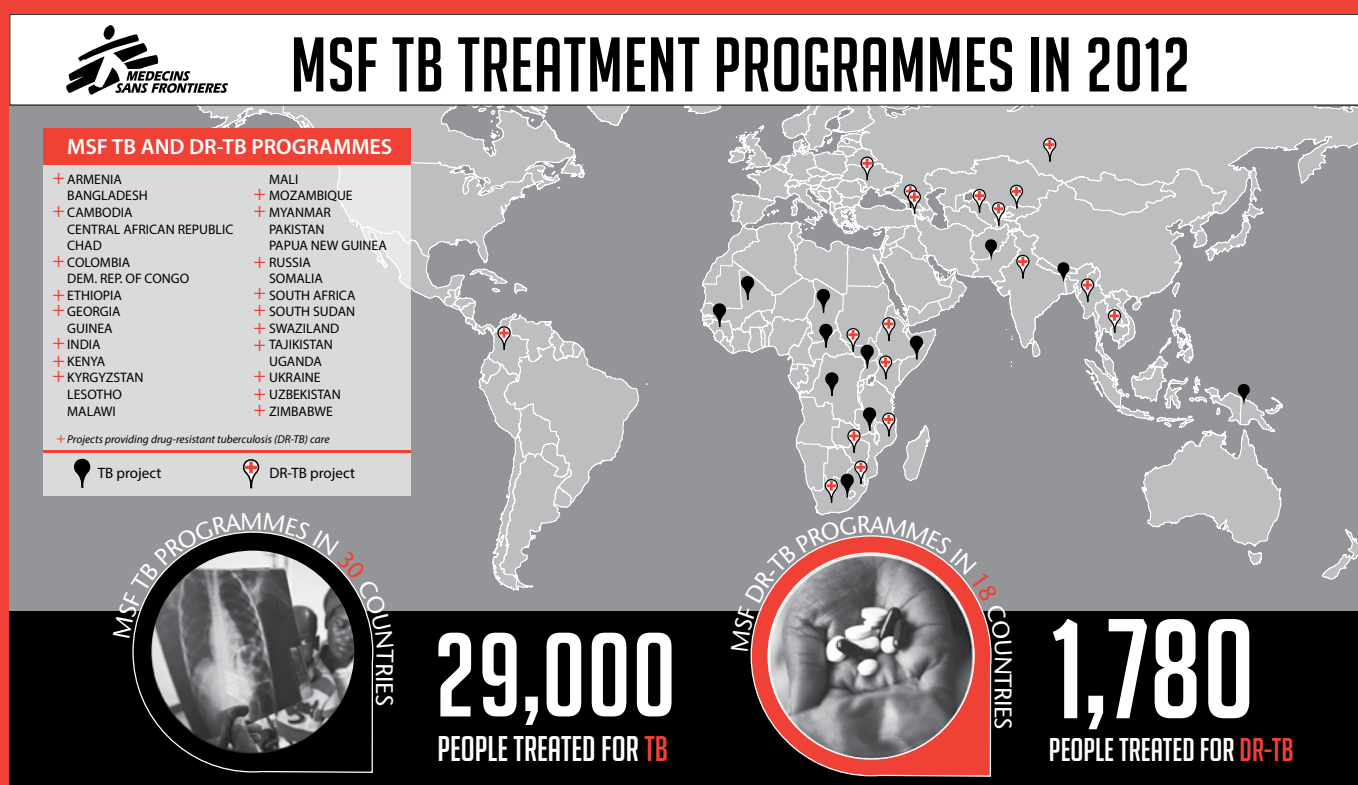
Drug-resistant tuberculosis (DR-TB) is used to describe strains of TB that show resistance to one or more first-line drugs, and is an umbrella term encompassing MDR-, XDR- and PDR-TB.

Multidrug-resistant tuberculosis (MDR-TB) is defined by TB that is resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs.

Extensively drug-resistant tuberculosis (XDR-TB) is caused by strains of MDR-TB that are also resistant to second-line drugs, including at least one from the class of fluoroquinolones, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).

The phrase '**totally drug-resistant TB (TDR-TB)**' has been used since late 2010 to describe a group of patients in India that have developed resistance to all drugs for which they were tested. However, this is not accepted WHO terminology, and these cases are officially defined as XDR-TB.

Polydrug-resistant TB (PDR-TB) is defined by TB that is resistant to more than one of the first-line drugs, but is neither MDR-TB nor XDR-TB.



MSF has been involved in TB care for 25 years. MSF started treating MDR-TB in 1999 and has grown to become one of the largest NGO providers of MDR-TB care. In 2012, MSF treated 29,000 patients for DS-TB in 30 countries, and 1,780 patients for DR-TB in 18 countries.

SOURCES AND PRICES OF DR-TB MEDICINES: SLUGGISH PROGRESS

- Additional quality-assured sources have become available for some medicines, pushing prices down by about \$1,000 per patient per course from 2012; however, the current recommended MDR-TB regimens remain prohibitively expensive, at \$3,000 to \$5,000 per treatment course
- For some key repurposed medicines, such as clofazimine and linezolid, affordable access to quality-assured products remains extremely challenging
- The biggest obstacles to affordable second-line TB medicines are the small size and fragmented nature of the DR-TB market, and high cost of patented drugs like linezolid
- The newest TB drug, bedaquiline, is priced at a level that sustains high prices for DR-TB regimens, and patents could further delay generic production of cheaper versions of this and other new TB drugs, particularly in combinations.

UNCOVERING THE EPIDEMIC: PERSISTENT GAPS IN THE DR-TB DIAGNOSTIC LANDSCAPE

The impact of potential game-changing advances in treatment can only be maximised with parallel advances in the diagnostic landscape for DR-TB. Speed and accuracy of DR-TB diagnosis has been boosted by the rollout of rapid molecular testing, but this new technology doesn't fill every gap in the complex diagnostic algorithm required to diagnose DR-TB. Scale up of an optimal package of diagnostic technologies and services will be a critical factor in reversing today's trends where people die while waiting for a proper diagnosis or are given sub-optimal treatment. Read MSF's brief, *Beyond the Microscope: addressing the critical need for TB diagnostics*, available at <http://www.msfaccess.org/content/beyond-the-microscope>



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Due to the limited capacity to diagnose (see box) and treat people with DR-TB and the structure of the DR-TB drugs market, the demand expressed to manufacturers for medicines has been historically small, even though the number of people who would be eligible for treatment each year, if they were properly diagnosed, is at least five times the number actually treated.⁴

Scale-up of the new rapid testing platform Xpert MTB/RIF is expected to peel back the lid on the scale of the epidemic,⁷ for example in Myanmar, where new rates of detection are beginning to outstrip current treatment capacity,⁸ and this trend may help increase the number of people treated with second-line TB drugs in the coming years.

The global MDR-TB market was estimated to be worth \$300 million in 2011, with only approximately \$170 million procured through the public sector.⁹ As a consequence, there are few

competitors, prices are still high and there is a limited number of quality-assured sources for DR-TB medicines.

The trend is largely positive, however. In recent years, the number of sources supplying quality-assured DR-TB drugs has increased. Several new sources for DR-TB medicines were approved by the WHO Prequalification (PQ) programme: three in 2011 (ofloxacin, levofloxacin, ethionamide), five in 2012 (ofloxacin, levofloxacin, moxifloxacin, ethionamide) and four in the first nine months of 2013 (prothionamide, amikacin, cycloserine, levofloxacin). In 2013 the joint Global Drug Facility/Global Fund Expert Review Panel, an additional mechanism for the assessment of drug quality, gave temporary permission to purchase one source of ofloxacin, two sources for moxifloxacin, two sources of cycloserine, two sources of prothionamide and one source of linezolid.

This year, there are only two medicines – clofazimine and terizidone – with a single quality-assured source, while last 30 per cent of the drugs profiled in this report were reliant on a single supplier for quality-assured products.

Nevertheless, the overall number of quality-assured sources remains limited, leaving the supply of quality-assured DR-TB medicines vulnerable to disruption. In some cases, multiple manufacturers are relying on the same source for Active Pharmaceutical Ingredient (API), as for cycloserine and capreomycin.

Furthermore, there is still minimal commitment by donors and governments, including middle-income countries, to purchase medicines which meet WHO standards. As a largely domestically funded market, the stringent rules around procuring quality-assured drugs are in many countries not in place, allowing cheaper, non-quality-assured versions of drugs to outcompete quality-assured versions – further fragmenting the market.

MDR-TB REGIMENS: PRICES DECREASING, BUT STILL VERY HIGH

Whereas first-line TB treatment is affordable, costing only \$22 per patient for a six-month treatment course,⁴ DR-TB treatment remains considerably more expensive. The exact price varies considerably, as treatment must be individualised according to a patient's drug resistance profile. Based on the 2011 WHO treatment guidelines, the two current recommended MDR-TB regimens – one with cycloserine, one with PAS, and both lasting 24 months and with eight months of injectable capreomycin – provide an approximate 'benchmark' price with which to assess MDR-TB regimen prices.

Since 2012, the overall cost for the current recommended regimen using cycloserine has decreased, from a range of \$3,953 to \$5,254 in 2012, to a range of \$2,909 to \$4,014 in 2013 (see Table 1). The overall cost for the current recommended regimen using PAS has also decreased, from a range of \$4,788 to \$5,786 in 2012, to a range of \$3,900 to \$5,148 in 2013 (see Table 2).

The main reason behind the drop is that increased competition over the past year has lowered prices for moxifloxacin and cycloserine, which dropped by 60% and 30% respectively. These are two of the four medicines that contribute heavily to the

overall cost of today's recommended DR-TB regimens; the others are capreomycin and PAS. No additional quality assured source of capreomycin or PAS/PAS-sodium were approved over the last year. The price of the PAS-sodium product dropped slightly, by 10%, compared to last year. Capreomycin's price increased by 4.5%, despite having five sources under evaluation by WHO PQ, three dossiers of which were already under assessment last year (the main barrier to approve new quality-assured sources relies in the complex process of API production). A future price drop can be expected once these new sources are qualified.

TABLE 1:

The cost in US\$ of an MDR-TB regimen lasting 24 months, including cycloserine and eight months of injectable capreomycin, using quality-assured medicines, based on prices provided for this report.

	LOWEST QUOTED QUALITY-ASSURED PRICES IN 2013 (US\$)		HIGHEST QUOTED QUALITY-ASSURED PRICES IN 2013 (US\$)	
	Unit price	Regimen price	Unit price	Regimen price
capreomycin 1g vial	5.557	1333.68	6.250	1,500.00
cycloserine 250mg capsule	0.408	881.28	0.520	1,123.20
ethionamide 250mg tablet	0.068	146.88	0.128	276.48
moxifloxacin 40mg tablet	0.680	489.60	1.460	1051.20
pyrazinamide 400mg tablet*	0.020	57.60	0.022	63.36
Total regimen cost		2909.04		4014.24

TABLE 2:

The cost in US\$ of an MDR-TB regimen lasting 24 months, including PAS and eight months of injectable capreomycin, using quality-assured medicines, based on prices provided for this report.

	LOWEST QUOTED QUALITY-ASSURED PRICES IN 2013 (US\$)		HIGHEST QUOTED QUALITY-ASSURED PRICES IN 2013 (US\$)	
	Unit price	Regimen price	Unit price	Regimen price
capreomycin 1g vial	5.557	1333.68	6.25	1,500.00
PAS 4gr sachet PAS-sodium 60% w/w granules 9.2g sachet	1.300	1,872.00	1.567	2256.48
ethionamide 250mg tablet	0.068	146.88	0.128	276.48
moxifloxacin 400mg tablet	0.680	489.60	1.460	1051.20
pyrazinamide 400mg tablet*	0.020	57.60	0.022	63.360
Total regimen cost		3899.76		5147.52

*Drug beyond the scope of this report, so prices were sourced from the GDF online catalogue at http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

It is possible to purchase a more affordable regimen, since some medicines are in some contexts interchangeable. For example, using kanamycin instead of capreomycin decreases the cost per patient by approximately \$1,000, while replacing moxifloxacin with levofloxacin will decrease the price by approximately \$500. However, cost considerations should not be the sole driving factor in selecting the regimen; safety profiles of medicines and resistance prevalence at country level are also key decision criteria.

REPURPOSED DRUGS: EXTREMELY LIMITED ACCESS

New approaches to treating DR-TB are being explored to optimise the use of existing medicines, including the testing regimens containing medicines used to treat other diseases, repurposed for use in DR-TB.

Repurposed medicines with proven efficacy in TB or potential efficacy in highly resistant TB cases can fill important gaps in DR-TB treatment, and are of increasing importance in both trial and operational research for DR-TB. But they need to be made accessible. These drugs are included in WHO treatment guidelines as “agents with unclear efficacy”.¹³ However, because they have no approved indication for DR-TB and they are not included in the WHO and/or countries’ essential medicines lists, accessing these drugs for DR-TB treatment is particularly difficult. Access for further research around optimal use of these products with other medicines is also very problematic.

These barriers do not apply to all repurposed drugs. Fluoroquinolones and the injectable agents are also used for DR-TB on an off-label basis, but there are no access issues associated with such use. Where there is concern is around access to clofazimine¹⁰ and linezolid,^{11,12} which are increasingly being used in treating DR-TB, although neither have an indication for TB. Clofazimine is used to treat leprosy, and linezolid is primarily used to treat hospital-acquired bacterial infections that mostly occur in developed countries.

CLOFAZIMINE

Securing affordable access to clofazimine is important because the drug is included in the STREAM clinical trial, which is assessing a nine-month DR-TB regimen that uses a combination of first- and second-line TB drugs. If proven effective, the nine-month regimen would cut the length of treatment by more than half and decrease its cost by about



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70% from \$2,909, the best possible benchmark price for a quality-assured current recommended MDR-TB regimen (see Table 1), to under \$900 (see Table 3). Such dramatic changes in regimen length and price would go a long way to removing key barriers to treatment scale up by governments and global health actors.

Despite the fact that the STREAM trial’s nine-month regimen for MDR-TB is showing promising results,¹⁴ Novartis has failed to take a proactive approach to clofazimine on the basis of unclear efficacy for DR-TB. This approach has made it very difficult for those who require it for research purposes to clarify the efficacy, and role of, clofazimine in new regimens. Access to the drug is similarly difficult for those requiring it for complicated DR-TB patients and operational research for STREAM. While price is currently not considered one of the main barriers to accessing clofazimine, Novartis’s approach to the supply of this

medicine, which can only be accessed for off-label use on named-patient basis, remains a key obstacle. There is no quality-assured generic producer.

LINEZOLID

For another repurposed drug, linezolid, new studies are adding to the evidence base of this drug in treating MDR-TB and in particular XDR-TB.¹⁵ MSF is using linezolid in several projects. A strengthened XDR-TB regimen pilot programme in Khayelitsha, South Africa, showed promising early clinical outcomes: as of the end of August 2013, 78% of patients have culture-converted – an early clinical outcomes are promising: as of the end of August 2013, 75% of patients have culture-converted – an early sign that treatment may be successful – and one patient has been clinically cured.¹⁶ Furthermore, results suggest that linezolid’s efficacy is not compromised when patients are also taking HIV treatment.¹⁷

But price is a major barrier. Until this year, Pfizer was the only quality-assured source for linezolid. The company's patent-protected monopoly in many countries allows them to keep prices prohibitively high. In South Africa, for example, where no generics are available, MSF pays ZAR676 (\$68) per 600mg tablet for the Pfizer product; at these prices, a six-month course of treatment for a DR-TB patient costs over ZAR121,680 (\$12,240), a high price for a single drug that, as with all DR-TB drugs, must be added to an expensive combination of other drugs. Private sector actors like MSF must pay more than double that price, which limits the ability to offer the drug to a greater number of patients.

In May 2013, however, Indian generic manufacturer Hetero became the first generic source temporarily eligible (until June 2014) for Global Fund procurement, based on the recommendation of the joint Global Drug Facility/Global Fund Expert Review Panel. The company is charging more than \$1,440 per patient for a six-month treatment course

(\$8 per pill). Hetero had previously indicated that it would price its generic linezolid at \$2.50 per pill,¹⁸ which would have pushed the cost down to approximately \$450 for six months' treatment. Since then, however, Hetero has taken advantage of its position as the only quality-assured generic source, more than tripling the promised price on the grounds of higher manufacturing costs owing to limited demand.

Government health programmes in South Africa, where more than 10,000 people a year are diagnosed with MDR-TB, could save over 70% on the cost of linezolid by overcoming Pfizer's patent barrier and accessing generic products. One key strategy that the government could consider includes fast-tracked registration of generic linezolid products in South Africa in anticipation of Pfizer's compound patent expiring in August 2014. Pfizer's secondary patents on linezolid in South Africa have lapsed due to non-payment of renewal fees, which means any registered generic competitor could launch upon expiration of the compound patent next year.

The capacity of generic competition to bring prices down needs to be harnessed. In 2014, additional quality-assured versions of linezolid should enter the US and European markets, creating the opportunity to improve supply and further decrease the price, at least in countries where Pfizer's patents do not exist or can be overcome. WHO should also encourage generic manufacturers to produce these needed medicines. But to date, neither clofazimine nor linezolid has been added to the WHO Essential Medicines List for DR-TB or to the Expression of Interest for the WHO prequalification programme. Adding clofazimine and linezolid to these lists with an indication for DR-TB is a critical step towards securing generic alternatives, adding the drugs to country treatment protocols and national procurement plans, and supporting the creation of a sustainable supply chain for DR-TB treatment.

TABLE 3:

The cost in US\$ of a shortened MDR-TB regimen lasting nine months, designed according to the STREAM trial regimen and using quality-assured medicines, based on prices provided for this report (regimen still under trial).

	LOWEST QUOTED QUALITY-ASSURED PRICES IN 2013 (US\$)		HIGHEST QUOTED QUALITY-ASSURED PRICES IN 2013 (US\$)	
	Unit price	Regimen price	Unit price	Regimen price
kanamycin 1g vial	0.800	96.00	2.580	309.60
clofazimine 100mg capsule	1.208	326.16	1.208	326.16
ethambutol 400mg tablet*	0.033	26.73	0.033	26.73
moxifloxacin 400mg tablet	0.680	367.20	1.460	788.40
pyrazinamide 400mg tablet*	0.020	27.00	0.022	29.70
prothionamide 250mg tablet	0.109	39.24	0.167	60.12
isoniazid 300 mg tablet*	0.020	4.80	0.022	5.28
Total regimen cost		887.13		1,545.99

*Drug beyond the scope of this report, so prices were sourced from the GDF online catalogue at http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

PHUMEZA TISILE: CURED OF XDR-TB, AND ADVOCATING FOR CHANGE

After enduring more than two years of a gruelling treatment regimen, which involved taking an estimated 20,000 tablets plus months of painful injections, 23-year-old South African student Phumeza Tisile has been cured of XDR-TB.

Diagnostics for drug-resistant forms of TB were not readily available in South Africa when Phumeza was initially diagnosed with TB. She therefore started the standard six-month regimen for drug-sensitive TB in the public sector, but her condition did not improve.

Following further lab tests, she was diagnosed with drug-resistant TB, and put on a recommended MDR-TB treatment regimen. When this regimen also failed to improve Phumeza's condition, further analysis of her sputum samples diagnosed pre-XDR-TB, and finally XDR-TB. Despite excellent adherence to her treatment regimen, the time required to obtain an accurate XDR-TB diagnosis meant Phumeza took drugs that were not effective for her for over eight months.

After an arduous journey, Phumeza has beaten the odds: only 13% of XDR-TB patients are cured by the treatment. But she lost a great deal along the way: she had to give up her studies during treatment, and amongst the many side effects that she suffered while on treatment, there is one she will have to live with forever: she is now permanently deaf, from a drug that her form of XDR-TB was resistant to from the start.

"Phumeza fought hard for this," her MSF doctor Jenny Hughes recalls. "She stuck to her treatment, even through the nausea and vomiting, even after she lost her hearing."

Phumeza has been using her experience to advocate for change on behalf of her fellow patients. Phumeza is the patient co-author of the **'Test me, treat me'** DR-TB manifesto, a campaign launched to pressure the TB community, governments and donors into ensuring universal access to DR-TB diagnosis and treatment, developing better treatment regimens, and providing adequate funding to do both.

As a committed TB activist, Phumeza is calling for access to drugs like linezolid, which offer one of the best hopes of successful treatment for XDR-TB patients, and for new regimens to be developed that are safer, shorter and more effective than those she and her fellow patients have had to endure.

"I had to take at least three medications, more than 20 tablets daily, supplements and injections. It is just too much. Many other patients will agree," says Phumeza. "It seems impossible until it's done."

Phumeza has also shared her experiences through MSF TB&Me blog (<http://blogs.msf.org/tb/>), a collaborative blogging project that allows DR-TB patients to share their stories and engage with an online community.

JOIN PHUMEZA AND THE FIGHT FOR BETTER DR-TB CARE

“ *I never thought this day would come – I've beaten XDR-TB! Getting cured at last is very exciting. It was scary at first. But you live in hope – hope that one day you will be cured. I didn't want to be a TB statistic and that kept me going.* **”**

PHUMEZA TISILE

SUPPORT THE 'TEST ME, TREAT ME' DR-TB MANIFESTO!
SIGN ON AT: MSFACCESS.ORG/TBMANIFESTO/



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NEW CHEMICAL ENTITIES: REGISTRATION AND AFFORDABILITY

The most momentous development for DR-TB treatment is the advent of the first new drugs in 50 years developed specifically to treat MDR-TB. These two novel drugs have the potential to greatly improve DR-TB treatment options.

One of the drugs, bedaquiline, was given conditional, accelerated US FDA approval in December 2012, based on phase IIb data. The second drug, delamanid, is still undergoing stringent regulatory approval at the time of going to print.

How accessible these new drugs will be made, and whether their potential will be maximised for new regimens for DR-TB, remains unclear. Speedy registration is one issue: outside the US, bedaquiline is so far only available through compassionate use or clinical access programmes (see box overleaf), although registration is underway in six countries.

Prices are another. This is a moment where bold action to slash high prices for DR-TB regimens would be welcome, but the pricing framework disclosed by Janssen for bedaquiline does not meet such expectations. The company has suggested its framework will attempt to balance a country's ability to pay with the burden of disease. Thus, a six-month treatment course will cost \$3,000 in countries in middle and upper middle-income bracket, compared to \$900 in least-developed and resource-limited countries. The \$3,000 price is completely unaffordable for any developing country, and the \$900 price keeps overall regimen costs – still likely to be thousands of dollars per treatment course – too high to facilitate urgently-needed treatment scale up. The company has not disclosed which price would be paid by countries that are classified as 'middle-income' and which have a high burden of TB, including high-burden countries like China, India, Ukraine and Uzbekistan.

High prices are likely to persist unless patent barriers are challenged and overcome. Unlike most existing DR-TB drugs (with the exception of linezolid), all of the new drugs are covered under patent protection. Multiple patent applications are underway or have been granted in several countries, including those with high burdens of disease.



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Patents in countries with generic manufacturing capacity will prevent companies from producing more affordable versions, and will even prevent them from exporting to countries where no such patent barriers exist. For these newer drugs, it will be therefore more difficult to replicate the effects that price-busting generic competition had on HIV treatment.²⁰

The patent landscape also indicates that secondary patents – additional patents other than the patent on the basic compound and that cover new uses, formulations or combinations and serve to block generic competition even after the original patent expires – are a threat to future generic production.

The compound patents of both bedaquiline and delamanid, if granted in developing countries, expire in approximately 2023. The patent terms could be extended, however, under supplementary protection or through secondary patents.^{22, 23} For example, secondary patents that have been filed for bedaquiline would extend the term of patent protection by at least four years until the end of 2027. Patents are also being filed on combination pills that include the new drugs in a fixed-dose combination together with existing medicines, which would be a serious barrier to the development of regimens combining new and repurposed TB drugs. Patent barriers even apply to drugs that are still in clinical development.

Otsuka's patents on delamanid cover not only the compound but also its intermediate, isomer, salt, ester and combinations.²³ A patent covering the pipeline drug sutezolid in combination with other pipeline investigational drugs may become a problem in developing optimal treatment regimens, for example.¹⁰⁴

If countries are unable to secure affordable access to newer medicines, governments like Brazil, India and Thailand should consider exercising their rights under international trade rules to overcome patent barriers, for example by issuing compulsory licences to enable production, domestic supply and export of more affordable versions. In any case, secondary patents, where possible, should be challenged to ensure that generic competition is not unnecessarily delayed through abuse of the patent system.

Looking beyond price, country preparedness could be another limiting factor for a rapid access to new drugs. In 2012, WHO set up the Task Force for New Drug Policies,¹⁹ which will issue a toolkit in October 2012 to help guide national TB programmes in the roll-out of new drugs and regimens for TB treatment at the country level. Key contents will include a checklist for country preparedness, requirements for monitoring & evaluation, and pharmacovigilance.

COMPASSIONATE USE: GETTING EXPERIMENTAL TREATMENTS TO PATIENTS WITH NO OPTIONS

Compassionate use programmes are intended to provide potentially lifesaving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists, or who cannot enter a clinical trial. Also called 'clinical access' or 'special access,' compassionate use became a common approach over the years to fight diseases such as cancer and HIV/AIDS, and represents a critical opportunity to help people who would otherwise die for lack of effective treatment options. The World Health Organization approved the application of this concept to DR-TB in 2008, taking into consideration new TB compounds under clinical development.¹⁹

The drug developer has the final decision on whether a drug will be supplied for compassionate use and under which conditions. Janssen has operated a compassionate use programme for bedaquiline* since 2011 and to date more than 120 patients have gained access to the drug through this scheme.

In South Africa, bedaquiline is now available for patients that have exhausted treatment options in four select clinical access sites; however, the cumbersome approval process for patients needing the drug can delay the initiation of XDR-TB treatment. MSF's experience in trying to secure compassionate use access to bedaquiline in Armenia, Colombia, Swaziland and South Africa has demonstrated that political will is required to ensure that this happens.²⁵

In Armenia (see Spotlight on page 17), MSF has been able to secure access to bedaquiline for 23 patients because this year the government adapted its national regulations to allow compassionate use of medicines in their country.²⁵ In Colombia and Swaziland, MSF is currently supporting national TB programmes in advocating for the inclusion of a regulatory framework for compassionate use. Still, the majority of the high-burden countries do not allow compassionate use, even when it is considered the last chance for patients to be cured.

Despite the published evidence on the potential efficacy of delamanid in MDR-TB,²⁶ manufacturer Otsuka has not yet initiated a compassionate use programme. With other new drugs in phase III trials, with results expected soon, there are a number of drugs that will soon make a compelling case for compassionate use.

Further guidance on compassionate use is expected from WHO soon in the programmatic guidelines to accompany the 2011 MDR-TB guidelines, which should help countries implement this important regulatory framework with benefits beyond the immediate goal of allowing access to bedaquiline (in the short term while registration is awaited in the country) and delamanid. There needs to be greater awareness of and political willingness to use this option to treat DR-TB patients failing on current treatments, as well as the necessary regulatory framework to allow it.

* Note that according to current WHO recommendations bedaquiline should no longer be reserved for patients with no other therapeutic options (i.e. through compassionate use), but should be used earlier in a patient's treatment course.



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R&D: BREAKTHROUGH DRUGS OFFER NEW HOPE, BUT SIGNIFICANT RESEARCH GAPS PERSIST

- For the first time in half a century, there is a relatively robust late-stage TB drug pipeline with several drugs showing promising results. Nevertheless, the long-term sustainability of the TB R&D pipeline is far from secure
- The current system for R&D favours the development of single drugs, but complete regimens are needed
- The specific needs of children with DR-TB and people co-infected with HIV and DR-TB remain neglected and require further R&D efforts.

THE PIPELINE: MORE ROBUST, BUT NOT ROBUST ENOUGH

For decades, research and development (R&D) for TB has been woefully neglected, with no new drugs for close to half a century and very little research to determine the best use of existing DR-TB drugs. This has meant that today's DR-TB treatment is largely based on experience and expert opinion rather than randomised clinical trials, leaving a number of 'grey areas' where expert opinions may be conflicting. In addition, the difficulty in accessing 'repurposed' drugs illustrates the lack of incentive to assess whether drugs that have been brought to market for other indications can also be used in DR-TB treatment.

With one entirely new drug having reached the market in 2013, and with one expected to follow shortly, at a first glance the R&D pipeline for tuberculosis is finally delivering. And indeed, the late-stage TB drug pipeline is fuller than it has been in decades.

Below is a list of new compounds that are currently in phase II or phase III trials:

- **Delamanid** is a nitroimidazole which recently received a negative opinion for registration with the European Medicines Agency (EMA).^{27, 28} A re-application is pending at EMA and their decision is expected by the end of 2013.²⁴ Registration applications are pending at the US FDA and Pharmaceutical and Medical Devices Agency of Japan.³⁶ A phase III trial is underway, as are paediatric open-label, uncontrolled pharmacokinetics and safety studies of delamanid in children from birth to less than 18 years of age (Trial 232), which will take place concurrently with a bioequivalence study to compare delamanid suspension to delamanid

50mg tablets in healthy adults.^{29, 30} No compassionate use programme is available.

- **PA-824** is a nitroimidazole developed by the TB Alliance which is currently being developed as part of a new regimen with two trials in phase II (NC002 and NC003).^{31, 32} The results of NC002 (a combination of PA-824, moxifloxacin, and pyrazinamide) are due end of 2013, with the potential for a phase III trial of this regimen to commence if these results are positive. There are no imminent plans to submit a dossier for registration of PA-824 as a single clinical entity, and no compassionate use programme is available.

- **Sutezolid** (PNU-100480) is an oxazolidinone developed by Pfizer over a decade ago for use in resistant gram-positive bacterial infections. Despite early evidence of activity against TB, the drug was left without significant development for over a decade. A phase II early bactericidal activity (EBA) trial has been completed, although the results have yet to be published. Pfizer's decision to abandon its entire anti-infectives R&D section has delayed the publishing of the data as well as the development of a formulation for sutezolid, adding further delay to this potentially useful drug being able to be used in the treatment of DR-TB. The drug was recently transferred from Pfizer to Sequella for continued development. The phase II EBA trial results need to be published. The phase IIb studies and the clinical development plan are being planned. Sutezolid has the potential for a compassionate use programme once further data are available.

- **SQ109** is an ethylenediamine which is being developed by Sequella. It is currently being evaluated in a phase IIa EBA study to determine safety, sputum clearance of mycobacteria, and pharmacokinetics of multiple doses of SQ109 alone or with rifampicin in patients with smear-positive pulmonary TB.³³ SQ109 has the potential for a compassionate use programme once further data are available.

- **AZD-5847** is an oxazolidinone being developed by Astra-Zeneca. A phase IIa study is underway to assess the EBA at four different doses and schedules in subjects with newly-diagnosed sputum smear-positive pulmonary TB. AZD-5847 has the potential for a compassionate use programme once further data are available.

Although these compounds in clinical development might hold the potential for a more promising future for DR-TB treatment than has been the case for decades, it would be premature to conclude that the long-standing neglect of R&D into TB had come to an end.

The drug pipeline for TB needs to be kept full with a range of different compounds in each phase of clinical development. According to the annual survey by the Stop TB Partnership Working Group on New Drugs,³⁴ there are no new compounds in phase I clinical development, and eight new compounds in late pre-clinical development. Given that a robust early stage development pipeline is the only way to ensure continued advances in DR-TB regimen development, this is a source of concern.

HISTORIC OPPORTUNITY SQUANDERED? THE NEED FOR COMBINATIONS

Above and beyond the lack of compounds in early stages of the R&D pipeline, other significant research gaps remain, so much so that the unprecedented opportunity presented by the availability of new TB drugs today is at a high risk of being squandered because of the current R&D environment.

Effective TB treatment requires a robust combination of different classes of drugs to be taken concurrently for prolonged periods of time – this prevents, or at least greatly hinders, the development of resistance to individual drugs. Simply adding the new TB drugs, bedaquiline and delamanid (if approved), to current WHO-approved regimens risks the rapid loss of their efficacy because the underlying regimens are still too arduous for patients: they will still contain toxic, burdensome medicines that must be endured for long periods of time, and patients who cannot tolerate them will be at risk for treatment interruptions and development of resistance.

To fundamentally change and improve DR-TB treatment, robust new regimens containing multiple novel and better tolerated drugs are desperately needed to completely replace the old, toxic drugs that will necessarily remain a part of the current recommended DR-TB regimens for the foreseeable future.

However, there is a deep lack of interest by industry to perform the collaborative research needed to develop new regimens, as opposed to individual drugs. If new molecules were combined earlier in the clinical research process, effective new regimens that are shorter and more tolerable could be made available to patients as soon as the drugs are registered. This would avoid the current situation whereby regimen-based research cannot start in earnest until each individual drug is well into the late clinical development stage, if not actually registered. Presently, clinical trials for new regimens are not completed until years after the individual drugs are registered.

In the immediate instance, this is the case with bedaquiline and delamanid. As MDR-TB is rightly considered as a serious public health threat by health authorities, bedaquiline was granted accelerated market approval for based on early development data collected through phase II trials. Bedaquiline and delamanid, as well as the other drugs in clinical development, are thus coming through the pipeline, or even to market, with little information on safety and efficacy relating to the use of these drugs in combination with other drugs. This means that clinicians in the field are in the dark about how to use these new drugs safely with other medicines. This in turn leads to a situation where these drugs could be used in settings without information on how to appropriately monitor adverse reactions in patients until phase III programmes deliver their complete outcomes. In the meantime, significant efforts towards pharmacovigilance will be required from countries which will be early dispensers of these new TB medicines.

More fundamentally, the problem lies largely with the current incentive system for R&D, which inhibits the collaboration and transparency that is critical to evaluating new drug-resistant treatment regimens. Companies are often unwilling to conduct pre-clinical studies and clinical trials to establish the efficacy of a particular drug or new drug combination against TB, or even to submit registration for a new indication of their drug based on trials financed and run by others. For them this holds potential risks and offers little benefit.

In order to sustainably overcome these R&D failings and ensure a full TB drug pipeline that results in effective, tolerable all-oral therapy, far more public investment is needed. Throughout the R&D process it is important to overcome the strategy of exclusivity and silos. There is an urgent need to incentivise collaboration between different R&D actors that are currently putting up barriers

to protect their realm, and to ensure that data is shared collaboratively for the purpose of exploring new regimens that can improve patient outcomes and shorten treatment, with the ultimate aim of developing new 'pan-TB' regimens that are suitable for both drug-sensitive and drug-resistant strains of the disease.

A key part of the solution will also involve delinking the cost of drug research and development from the price of medicines, and promoting collaborative open innovation and access to the fruits of R&D. Public investment should be deployed through a mixture of classic push funding (e.g. grants) as well as innovative pull incentives (e.g. milestone and end stage prizes). One of the strategies that has worked in many other fields of technology (namely aeronautics and consumer electronics) is to pool intellectual property to remove barriers for subsequent innovations and development, like fixed-dose combinations. These 'patent pools' have the potential to function as a 'one-stop-shop' and therefore simplify and encourage further development of technologies that are covered by more than one patent from more than one actor. As MDR-TB regimens must be developed from drugs with multiple patents from multiple different developers, pools may be well suited for MDR-TB regimen development.



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WANTED: COMBINATION REGIMENS THAT FULFIL THE FOLLOWING CONDITIONS

MSF gathered a group of experts in July 2012 that outlined eight key principles for designing future DR-TB regimens to ensure new drugs are used to their maximum advantage.³⁵

Regimens should:

- contain at least one new class of drugs;
- be broadly effective against MDR and XDR strains;
- contain a minimum of three and a maximum of five effective drugs, each from a different drug class;
- be an oral regimen (i.e. not include an injectable agent);
- have a simple dosing schedule;
- have a good side-effect profile that allows limited monitoring;
- have a maximum duration of six months; and,
- have minimal interaction with antiretroviral drugs to treat HIV.

These principles should be used to help ensure that future regimen development maximises the potential of new compounds while addressing the individual, programmatic and scale-up issues that plague the current regimen.

CLINICAL TRIAL LANDSCAPE FOR DR-TB REGIMENS

A number of clinical trials are underway to assess optimal combinations of re-purposed and new TB drugs.

Although there are a number of promising regimen trials, the scope and slow progress of these trials are concerning. Some trials, including the Nix trial, plan to only include those people with XDR-TB, however people with pre-XDR- and MDR-TB are also in desperate need of improved regimens. These trials should include a plan to rapidly incorporate broader populations of DR-TB patients, especially if initial safety of the regimen is assessed. A greater sense of urgency is needed in bringing these trials forward to develop much-needed new regimens. Better cooperation is required from manufacturers, as the lack of cooperation is also hindering trial progress. Currently, none of these trials have a paediatric component, meaning that, yet again, the needs of children will be excluded from new treatment developments.

Below is an overview of ongoing initiatives. Each trial listed here includes patients co-infected with HIV, but with different inclusion criteria:

- **STREAM Trial:** This is a USAID-funded, Union-sponsored and MRC UK-implemented randomised clinical trial looking at a nine-month combination of existing TB drugs for the treatment of MDR-TB.³⁷ The study regimen is ethambutol, pyrazinamide, moxifloxacin and clofazimine throughout, supplemented by kanamycin, prothionamide and 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. Recruitment has started in Ethiopia, Vietnam and South Africa and the results may be ready by 2018.
- **NC002 Trial:** This is a TB Alliance-funded phase II trial looking into the combination of moxifloxacin, PA-824 and pyrazinamide in patients with DS- and DR-TB.³¹ The trial includes patients co-infected with HIV. The trial has been completed and the results are expected in early 2014.
- **NC003 Trial:** An EBA study, funded by TB Alliance, looking at combinations of PA-824 with bedaquiline, clofazimine and pyrazinamide.³⁸ The trial includes patients co-infected with HIV. Results are expected towards the end of 2013. Combinations showing promise will be taken forward for phase IIb trials.
- **Nix TB Trial:** This proposed open-label study proposed by TB Alliance involves bedaquiline given only with other new drugs (PA-824 and an oxazolidinone) to patients with XDR-TB, including patients co-infected with HIV.
- **Marvel TB Trial:** A proposed phase II trial, currently undergoing final protocol confirmation, looking at the efficacy and toxicity at two months of combinations of bedaquiline, sutezolid, PA-824, SQ-109, pyrazinamide, levofloxacin and clofazimine for MDR-TB treatment.³⁹ The trial includes patients co-infected with HIV.

SIGNIFICANT GAPS IN RESEARCH PERSIST FOR VULNERABLE POPULATIONS

The needs of children and people living with HIV continued to be neglected by ongoing initiatives in research and development for tuberculosis.

A dearth of research to address the needs of childhood TB, and DR-TB in particular, is partly because little is known about the disease burden in children. Diagnostics appropriate for paediatric use are sorely lacking, which contributes to the problem and obscures the depth of treatment needs. The market for paediatric TB medicines in 2011 was estimated to be less than \$10 million.⁴⁰

According to WHO, children account for around half a million new TB cases and 74,000 deaths from TB each year.⁴⁶ But the figure is known to be an underestimation – it doesn't include TB-related deaths in children infected with HIV, which are classified as HIV-related deaths. No data exists regarding the prevalence of DR-TB in children.

The WHO MDR-TB programmatic guidelines released in 2011 did not provide guidance on dosing or the use of DR-TB drugs in children and adolescents. The updated WHO childhood TB guidelines expected by the end of 2013 are expected to give more guidance on the dosages required for second-line drugs.

Even when recommendations are in place, the paucity of safety, efficacy and pharmacokinetic data available for drugs used to treat DR-TB in children and the lack of paediatric formulations makes implementation challenging. Only three medicines featured in this report (amikacin, levofloxacin and linezolid) have been developed as paediatric formulations, but only for uses other than TB and for much shorter treatment courses than required for TB. None of the paediatric versions are widely available, nor are they included in the GDF product catalogue, which means that treatment providers cannot purchase them through the GDF.

Treatment providers who attempt to treat children must do so by manipulating adult formulations, such as breaking or crushing tablets to approximate the required dose. This carries a major risk of over- or under-dosing a child. In addition, safety and efficacy data in children have not been established for the majority of the medicines used in DR-TB treatment.

Delamanid is the only new drug in the pipeline that has started trials for use in children, and none of the new regimen trials for TB have a paediatric component. This means that children will have to wait longer to benefit from any new development in new drugs or new regimens.

People co-infected with HIV represent another population neglected by TB R&D initiatives. The interactions of DR-TB drugs with HIV medicines are also largely unknown.⁴² This research has not been a priority for HIV drug developers because co-infection with TB is now uncommon in wealthy countries. This is particularly problematic given that TB is the biggest killer of people living with HIV today.⁴³

For many DR-TB medicines, crucial research is lacking. Kanamycin, amikacin and capreomycin all have the potential for renal toxicity, as does tenofovir (the backbone of the WHO-recommended first-line HIV treatment regimen). It is unclear what additional monitoring may be needed for the potential additive renal toxicities of these drugs. Medicines from the fluoroquinolone class – moxifloxacin, levofloxacin and ofloxacin – are thought to interact with crucial protease inhibitors like lopinavir and atazanavir (both part of second-line HIV regimens). Drug interactions are also predicted between ethionamide and prothionamide and antiretrovirals such as nevirapine and efavirenz, and there is very little knowledge about possible interactions for other medicines, such as cycloserine, terizidone and PAS. People living with HIV desperately need updated, less toxic regimens, with more acceptable drug-drug interactions with antiretroviral therapy.



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WHAT NEEDS TO HAPPEN

ENSURING AFFORDABLE ACCESS TO QUALITY-ASSURED DR-TB MEDICINES

The inadequate ability to diagnose DR-TB and insufficient numbers of patients on treatment means that demand for DR-TB drugs is low, not least for medicines which meet WHO standards. Therefore, there is little incentive either for new producers to enter the market or for existing producers to invest in meeting WHO quality standards or increase production capacity.

This creates a vicious circle, as limited drug supplies and expensive medicines in turn contribute to hindering the scale up of DR-TB treatment. Supply insecurity due to delivery delays or interruptions, together with sometimes weak capacity at country level to

manage accurate consumption forecasting and to put new DR-TB patients on treatment, are a detriment to treatment scale-up in a number of contexts. And worse, supply problems have results in acute stockouts of drugs in some areas.

The market for DR-TB drugs is not only low in volume, but also remains very fragmented for a number of reasons, including insufficient pooled demand for quality-assured drugs that meet WHO standards, the different quality standards for medicines applied by national medicine regulatory authorities, as well as the high degree of variation between regimens used by country programmes.

Economies of scale and further price decreases could be possible if countries with high burden of disease, including all middle-income countries, would pool their demand for DR-TB drugs and commit to use only medicines that meet WHO standards. A drug which complies with WHO quality standards is more expensive to produce than a non-quality-assured drug, increasing the cost to countries which prioritise quality-assured products. However, a stronger, more consolidated market without patent barriers must be developed, especially for the new TB drugs, if prices for quality-assured medicines are to come down to affordable rates.

POOLED PROCUREMENT

By aggregating individual countries' demand, pooled procurement has the potential to bring a global solution to problems of supply disruption of API and/or finished formulations, and to favour the economies of scale needed to decrease prices and increase access to quality-assured medicines.

Orders for DR-TB drugs placed with GDF are often small, do not reach optimum production quantities, and need to be pooled before manufacturers will produce a new batch. This process, coupled with the consolidation of several products within the same shipment and the need for up-front payment before orders are processed, leads to long standard lead times of four to six months from order placement. Late payments and inadequate procurement planning by countries can lead to even longer lead times and even stock ruptures. Support to build up in-country drug procurement and management capacities, as well as improved cash flow between donors and countries, could improve the situation.

GDF, with UNITAID support, has taken some steps to address these issues, including implementation of a limited stockpile to be able to expedite shipments in emergencies. GDF is currently working with partners like Global Fund and other donors to develop a rapid response mechanism, increase the size of current stockpile and implement some more flexible procurement funding facilities to overcome current supply chain barriers: this could significantly shorten lead times and offer the needed flexibility to adequately support in-country scale-up challenges at the time of Xpert MTB/RIF roll-out.

In a fragmented and volatile market, pooled procurement could facilitate global solutions to supply disruptions, as very few countries have the capacity or resources to identify new sources of quality-assured medicines on their own. However, a pooled procurement mechanism on its own will not secure and maintain a market of affordable quality-assured drugs, unless the size of the demand it covers is substantial.

The problem of too few quality-assured sources for international supply could be partially resolved by linking funding to procurement for quality-assured medicines. While the Global Fund requires medicines procured by the DR-TB programmes to meet WHO quality standards, thus contributing to pooled demand for quality-assured medicines, other donors such as the World Bank do not yet set specific quality criteria.

When weak regulatory authorities allow marketing of products that do not meet WHO quality standards but are nevertheless procured by national tuberculosis programmes, quality of medicine is clearly not being prioritised enough (see box overleaf). To date, institutions, governments and WHO have not done enough to address this serious issue.

QUALITY: A CRITICAL QUESTION FOR DR-TB MEDICINES

The use of poor quality medicines to treat TB is one of the key contributing factors fuelling drug resistance and increasing the burden of MDR- and XDR-TB.

One reason is that the capacity of national medicine regulatory authorities is highly variable between countries, and many have difficulty assessing quality when it comes to production and importation of medicines. Stringently regulated countries are able to evaluate adherence to WHO standards,^{9, 44} for quality assurance, whereas weaker regulatory authorities do not necessarily have the human and financial resources to ensure all required quality criteria are met.

In addition, quality standards for production differ from country to country. For example, India produces many medicines that meet WHO standards and are eligible for procurement by major donors, such as the Global Fund and UNITAID. However, quality procedures differ depending on whether the purchases are covered by domestic funding or Global Fund grants, with WHO prequalification required for some products but not for others.⁴⁵ In addition, there is considerable confusion between the terms that define the quality of a source used in tenders for the procurement of TB drugs.

Securing the quality of DR-TB medicines also implies securing the quality of the active pharmaceutical ingredients (API) they contain. API quality is directly related to the quality of the finished product, and APIs weigh heavily in the production costs of a finished product. The main bottleneck preventing more quality-assured sources of kanamycin and capreomycin is the complex manufacturing process of the APIs for these drugs; worldwide production is today controlled by the few manufacturers who have adequate technical capacity.

There are currently only a few API sources available for DR-TB drugs that meet WHO quality standards. For example, the four manufacturers producing cycloserine in blisters are all using the same quality-assured API source, thus increasing the vulnerability of the supply.

It is essential to start considering ways to increase access to quality-assured affordable APIs for DR-TB drugs. In November 2010, WHO developed the Active Pharmaceutical Ingredient-Prequalification (API-PQ) procedure in response to calls to ensure that APIs used in essential medicines were of acceptable quality. The API-PQ procedure first verifies sources of API that meet international standards, and then publishes details about

the manufacturers on the WHO Prequalification of Medicines website.ⁱ This list is intended to make it easier for manufacturers to identify APIs of verified-quality. Since the commencement of the API-PQ procedure nearly three years ago, 43 APIs have been prequalified, including 13 APIs used in the treatment of TB. Another dozen anti-TB APIs are under assessment.

Although major donors are increasingly recognising the importance of quality standards, the insistence on API quality and manufacturing standards is often not vigorously verified. In both countries producing API and countries buying API to produce a finished product, regulations to control the API manufacturing process and its quality are either new, underdeveloped or absent. This allows drug manufacturers to use API sources that may be much more affordable, but which are of substandard or unverified quality. Not only does this have an impact on patient safety and treatment, it perpetuates the struggle that manufacturers producing quality-assured medicines face in competing with products that might be cheaper, but that use API of unverified quality.

ⁱ http://apps.who.int/prequal/info_applicants/API_PQ-List.htm

THE ROLE OF MIDDLE-INCOME COUNTRIES

The market for DR-TB drugs is largely concentrated in the BRICS countries. Russia, India, South Africa and China account for 60% of all notified DR-TB cases among the 22 high-burden countries.⁴ These countries also have the largest population of undiagnosed and untreated DR-TB.⁴

Procurement decisions made in these countries will have a considerable impact on the future shape of the market but have the potential to reduce average global costs for both diagnostics and treatment. If these countries committed to using DR-TB medicines that meet WHO quality standards, global demand for these would

be consolidated, likely leading to more quality-assured suppliers of both API and finished formulations entering the market.

These countries also play a major role in manufacturing of both API and finished formulations. 80 – 85% of active pharmaceutical ingredients, including for second-line DR-TB drugs, are produced in China, largely due to its advanced fermentation technology and cost position for manufacturing.⁹ India is a major producer of finished TB formulations. Yet not all medicines produced and marketed in these countries meet WHO quality standards.⁴

Finally, these countries should develop common approaches to tackle, at the national level, the intellectual property and regulatory barriers that interfere with access to low-cost generic versions of new medicines. Competition is the only sustainable route to overcome unaffordable prices charged to middle-income countries by multinational pharmaceutical companies. Such efforts would not only improve access to treatment in the BRICS, but would also benefit other developing countries.

ENSURING R&D INITIATIVES DELIVER FOR PATIENTS IN NEED

Today's treatment is expensive, complex, toxic, and insufficiently effective, and the need for better, shorter regimens is pressing. All donors and governments should therefore substantially increase public investment for R&D in TB.

Yet the 2013 figures from the Treatment Action Group's annual survey of TB research⁴⁶ show that for the first time, funding dedicated to TB R&D is actually declining – down by \$30 million to an annual investment of \$627 million. This represents only 31% of the needs, and leaves a shortfall of \$1.39 billion compared to funding targets set by the Stop TB Partnership. The survey results point to wavering commitments from the private sector placing greater pressure on public sector donors, just as they begin to face unprecedented budget cutbacks.

There is a need for a wider funding base too, as the almost half (45%) of TB R&D funding comes from two organisations, and the vast majority (78%) comes from the first 10 funding sources. More governments need to invest, particularly emerging economies which face a large domestic burden of disease.

Ensuring this investment is used to create the biggest impact for patients with TB, by embracing new models of R&D funding based on open collaborative approaches, the pooling of intellectual property and the structuring of incentives so as to prioritise the development of drug regimens rather than single drugs or agents will be critical. This public investment should be protected through specific provisions that ensure that the full benefits of innovation developed with public funds are enjoyed by the public.

Enforcement of intellectual property rights does not provide an incentive to encourage development of appropriate regimens that can treat neglected diseases like TB. Pharmaceutical companies should therefore collaborate with, rather than fight, efforts to create R&D incentives outside of the patent system for the development of affordable and appropriate new drug combinations. What is needed now are treatment regimens to effectively treat all forms of TB. The current business model that is built on exclusivity, rather than on collaboration and openness, is not capable of delivering the desired outcome. New, open approaches are needed in order not only to produce drugs but effective, safe, easy-to-tolerate, short and all-oral treatment regimens.

SECURING THE FUNDING BASE

In addition to securing greater investment in R&D, more funding for DR-TB diagnostics and treatment scale-up is needed. According to the WHO Global TB Report 2012, an annual \$3 billion funding gap will persist out of the \$8 billion needed per year between 2013 and 2015 to fight TB in low- and

middle-income countries, unless national and international funding is increased.

The largest TB donor, the Global Fund to fight AIDS, TB, and Malaria, estimates the costs of combating TB and DR-TB over the next three-year replenishment period (2014 – 2016) to be \$15 billion

for the 118 countries that are eligible.⁴⁷ Should the GFATM be fully-funded at its December 2013 replenishment conference, an estimated 17 million people with TB and DR-TB could receive treatment, compared to a flat-funded scenario where three million would have to go without.

SPOTLIGHT ON ARMENIA

In 2013, the National Tuberculosis Programme (NTP) of Armenia, supported by Médecins Sans Frontières, was confronted by growing numbers of XDR-TB patients for whom the WHO-recommended treatment for drug-resistant tuberculosis was failing. In response, the NTP established a mechanism to access experimental drugs for compassionate use in treating XDR-TB.

The NTP formed an Ethics Committee to review bedaquiline use for TB patients in November 2012. Importation of bedaquiline on humanitarian grounds was approved in January 2013, whilst waiting for the formal introduction of legislation on compassionate use of experimental drugs. An external expert medical committee reviewed the first case in January 2013, and the Armenian NTP presented the case to the manufacturer in February 2013.

Between February 2013 and July 2013, 23 out of 28 patients were approved to receive bedaquiline under compassionate use by both the expert committee and the manufacturer.

“ Armenia showed that it is feasible for NTPs to implement mechanisms allowing access to experimental drugs for patients in need. Putting in place the required regulatory framework and technical support can be a lengthy process. Despite the challenges, accessing experimental TB drugs has given new hope to patients who have no further therapeutic options. ”

DR. SAIFUL QAYYUM, MEDICAL COORDINATOR, ARMENIA, MÉDECINS SANS FRONTIÈRES



In addition to bedaquiline, all patients needed linezolid and 13 out of 23 also needed imipenem. Both drugs posed particular challenges: there are significant side effects for linezolid and imipenem requires twice-daily intravenous administration. Enhanced monitoring requirements for bedaquiline and linezolid proved challenging under programmatic conditions.

The NTP proved flexible and adopted an innovative approach on the administration of these drugs in ambulatory settings, adapting informed consent and counselling for the new drugs, and unresolved questions on the duration of individual drug therapy.

SPOTLIGHT ON INDIA

India currently faces enormous challenges in controlling an unchecked drug-resistant tuberculosis epidemic, with a large burden of cases and an increasing number of drug-resistant strains. According to WHO, India had about 66,000 MDR-TB patients in 2011, but only 3,384 patients were put on treatment.⁴

One of the main contributing factors to the epidemic is the fact that India's private health care sector is allowed to diagnose and treat TB without adherence to any standard protocols. Antibiotics and anti-TB medicines are widely available for sale over the counter, without adequate system to ensure adherence to treatment. Chronic misuse of the medicines is fuelling drug-resistant TB in the country. As a result, the Indian context is very unique in terms of baseline drug resistance profiles. Especially notable is the high level of baseline resistance to fluoroquinolones, and this occurs independent of previous exposure to TB treatment.

An effective response to the DR-TB epidemic must include a new rational approach to treatment, and some encouraging steps are being undertaken. The government of India has already made the notification of all TB cases mandatory for all private practitioners.⁴⁸ Next, India's National TB programme is developing a plan to make quality-assured anti-TB drugs available to all citizens free of charge. In addition, the national TB programme is expected to take control of all TB medicines in the country, and to restrict over the counter sale of TB drugs.

According to the proposed plan, the drugs would be available only to patients enrolled in the national TB programme and to those who obtain vouchers from qualified private practitioners, who in turn can obtain the vouchers after notifying the patient to a national registry.⁴⁹ If these measures are implemented, the result should be better treatment outcomes and better epidemiological control of the disease, which will help stem the emergence of drug-resistant TB.

However, whatever gains are made in rationalising treatment protocols will be lost if problems with drug procurement are not also solved. This year, India experienced stock outs of DR-TB drugs across the country. Under India's public TB treatment programme, the central government is responsible for buying drugs and distributing them to the states, which then provide treatment. The stock outs are related to long-standing problems with the drug procurement agency that supports all public health programmes – leading to chronic and deadly delays in the supply of drugs.

Stock outs of DR-TB drugs have been consistently reported in a number of Indian states since May 2013. The mismanagement in the procurement of DR-TB drugs and stock out at facility levels have increased concerns regarding the growing levels of drug resistance in the country.⁵⁰ MSF has called for the Indian government to urgently address the issue of chronic stock outs for TB drugs.⁵¹

“ *A continuous, sustainable supply of quality-assured medicines is vital for TB patients to have even half a chance of being cured. I feel powerless because we don't have the medicines to treat. It's just not good enough that India talks of scaling up DR-TB treatment, but finds the medicine cabinet empty at a time when people diagnosed with DR-TB are most desperate to get the medicines that can treat them. The Government must act now to address this dire situation.* **”**

DR. HOMA MANSOOR, TB MEDICAL REFERENT, INDIA, MÉDECINS SANS FRONTIÈRES



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SPOTLIGHT ON SOUTH AFRICA

South Africa has a high-burden of DR-TB, with over 10,000 new cases of MDR-TB diagnosed each year and just over half receiving treatment. The increased availability of Xpert MTB/RIF machines in South Africa means patients are being diagnosed more rapidly and starting on DR-TB treatment much more quickly than before, but this poses a threat to the capacity of the health system to handle higher case loads.

MSF has started piloting decentralised care for DR-TB patients in Khayelitsha in 2007, in order to offer an alternative to compulsory hospitalisation, and provide evidence that patients could start treatment faster and relieve overburdened health systems through a community-based approach to treatment. This model has proved successful and is now being piloted more widely by the Department of Health in Cape Town. However, despite decentralisation of services to increase diagnosis and treatment initiation, one of the ongoing challenges in DR-TB care is helping patients complete a full treatment course. Due to the high number of debilitating side effects and the high HIV co-infection rate, patients with DR-TB may take in excess of 15 tablets per day to manage all of these conditions. MDR-TB patients also need to endure months of excruciating injections. Patients urgently need better drug regimens that are more efficacious, require fewer pills, and have fewer side effects; this in turn would enable decentralisation programmes to be rolled out more easily.

A further complicating factor for patients in South Africa is that TB treatment is not always accessed at the same facility as HIV treatment. Given the high burden of HIV/TB co-infection in South Africa, efforts should be made to consolidate HIV and TB points of care.

New, more effective and tolerable DR-TB regimens are on the horizon, but patients in South Africa may have a long wait before they are made available locally. The Medicines Control Council (MCC) of South Africa typically takes a minimum of two years to register a new drug, which could delay use of these newer treatments.

While the MCC approved a “clinical access” programme for the new TB drug bedaquiline in January 2013, registration is undergoing. Through the clinical access programme, bedaquiline is now available for patients that have exhausted treatment options in four select sites in South Africa, though the cumbersome approval process for patients needing the drug can delay the initiation of XDR-TB treatment.

“*In South Africa the sheer magnitude of the MDR-TB epidemic alone warrants renewed commitment from the Department of Health and the MCC to allow patients to receive the best possible treatment as soon as possible. Newer drugs offer the opportunity to save lives, and while regulatory review is essential, increased patient access is urgently needed.*”

**DR. VIVIAN COX, DEPUTY MEDICAL FIELD COORDINATOR, SOUTH AFRICA,
MÉDECINS SANS FRONTIÈRES**



Drug stock outs pose additional risks to DR-TB treatment adherence and success in South Africa. 40% of the 70 facilities surveyed by MSF and TAC during May 2013 in the Mthatha catchment area of Eastern Cape Province had experienced HIV or TB drug stock-outs, or both. At 24% of the affected facilities, medical staff were forced to send patients home without treatment because the facilities experienced stock-outs of essential HIV and TB drugs. These stock-outs were reported to last, on average, 45 days at a time and remain almost as common and severe as they were when the problem was investigated five months previously.⁵²

Another issue for the South African government to address in order to effectively respond to the DR-TB epidemic is the question of patent barriers. These are preventing affordable access to linezolid, and must be urgently and appropriately addressed. The country's Department of Trade and Industry has shown its intention to improve processes for issuing compulsory licences in its Draft National Policy on Intellectual Property – a reform that, if implemented, may prove critical in accessing newer DR-TB drugs at affordable prices.

RECOMMENDATIONS

Affected country governments:

- ❖ Should increase DR-TB diagnostic capacity and scale-up of DR-TB treatment, and make improvements in procurement and supply systems to prevent stock outs of TB and DR-TB medicines
- ❖ Should strengthen the national regulatory framework, commit to use medicines which meet WHO standards (both for active pharmaceutical ingredients and for finished products) and pool demand for quality-assured medicines to secure the market, enable economies of scale and decrease prices
- ❖ Should establish a framework for compassionate use programmes
- ❖ Should implement the WHO interim guidance on the use of bedaquiline
- ❖ Should regulate access to DR-TB medicines in order to preserve their efficacy and avoid fuelling resistance, including among the private sector
- ❖ Should ensure national legislation appropriately incorporates intellectual property flexibilities allowed under TRIPS, and should make full use of TRIPS flexibilities to ensure affordable access to new TB drugs
- ❖ Should invest in R&D for new TB drug regimens, especially through alternative models to incentivise drug development that de-link the cost of R&D from the final product price
- ❖ Specifically BRICS countries should use the upcoming BRICS health ministerial meeting in January 2014 to further already stated commitments⁸⁴ on scale-up and innovation, but also to take steps to help lower-income countries.

The Global Drug Facility:

- ❖ Should continue to publish prices of medicines on its website in order to improve transparency
- ❖ Should finalise the expansion of the existing rotating stockpile to decrease the time it takes for countries to receive medicines for all orders, and not only emergency ones
- ❖ Should further develop a strategic revolving fund with international donors to provide manufacturers a financial guarantee to secure the production and supply of second-line TB drugs
- ❖ Should work towards worldwide access to additional quality-assured sources of clofazimine and linezolid

- ❖ Should continue to work with non-donor supported countries, including middle-income countries, to increase procurement of quality-assured medicines.

The World Health Organization:

- ❖ Should promote the use of quality-assured medicines at country level
- ❖ Should include all DR-TB drugs in the WHO Essential Medicines List and in the Expression of Interest list of the WHO prequalification programme
- ❖ Should ensure a comprehensive access and supply strategy for DR-TB medicines, which includes the removal of off-label use barriers by registration of TB indications for all medicines, including clofazimine and linezolid
- ❖ Should, through its new TB drugs taskforce, issue a statement on the need for registration for a TB indication for repurposed drugs including clofazimine and linezolid, and provide guidance on the evidence accrued and needed to obtain a TB treatment recommendation
- ❖ Should advocate and facilitate interventions to address intellectual property barriers associated with new TB drugs
- ❖ Should support the rapid evaluation of shorter treatment regimens, give timely advice on the use of new effective compounds, and support the development of new optimised regimens to treat DR-TB, in particular those looking at alternative models to incentivise drug development that de-link the cost of R&D from the final product price
- ❖ Should give guidance to countries about initiating a compassionate use programme and facilitating registration and appropriate scale up of the new compounds

Donors:

- ❖ Should increase financial support for DR-TB diagnostics and treatment scale-up, including through the largest funder for TB programmes, the Global Fund to fight AIDS, Tuberculosis and Malaria
- ❖ Should promote and monitor the use of quality-assured medicines at country level by harmonising quality criteria for procurement

- ❖ Should support research to define a better and shorter DR-TB treatment regimen with the inclusion of newer drugs, including through alternative models to incentivise drug development that de-link the cost of R&D from the final product price.

Pharmaceutical companies:

- ❖ All companies must invest in R&D to advance clinical development of new drugs to address TB and work with donors and developing countries to develop R&D programmes which prioritise regimen development
- ❖ **Janssen** should ensure more affordable access to bedaquiline in all low- and middle-income countries by issuing a voluntary licence to encourage low-cost generic production, or by offering a low price that includes middle-income countries
- ❖ **Otsuka** should develop a compassionate use programme for delamanid, and a strategy that ensures rapid registration and affordable prices for delamanid in low- and middle-income countries
- ❖ **Novartis** should remove barriers to off-label use of clofazimine, whether for research purposes or for patients with limited treatment options, by filing for a TB registration, and by increasing production to meet projected demand or by expediting technology transfer to another company
- ❖ **Pfizer** should remove barriers to off-label use of linezolid by filing for a TB registration, and should reduce its price by not enforcing patents, particularly secondary patents, that may block entry of low-cost generic versions in low- and middle-income countries
- ❖ **Hetero** should offer linezolid at the price of \$2.50 per tablet quoted in 2012, and should neither file nor enforce secondary patents on a generic version of linezolid
- ❖ **Sequella** should ensure that the development of sutezolid resumes its progress, including by manufacturing sufficient quantities of the product, by commencing a phase IIb trial in a timely manner, by making the compound available for research for other combination trials, and by publishing toxicity information and 2009 phase IIa data
- ❖ **AstraZeneca** should ensure that the development of AZD-5847 continues and that it is made available for other combination trials.



METHODOLOGY

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

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. In addition, for medicines with fewer than two generic quality-assured sources available, such as for linezolid and moxifloxacin, manufacturers with US FDA tentatively approved products were included. The data were collected up to August 2013.

PRICE INFORMATION

Prices are listed where manufacturers agreed to share information. A number of manufacturers, including Bayer, Glenmark, Lupin, Meiji, Novartis, Pfizer, Sandoz and Teva did not have prices available or did not agree to publish prices, and no responses were received from Biocom, Cadila, Chao Center Purdue, and Pharmathen Hellas.

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 received in currencies other than US\$ were converted on 12 August 2013 using the currency converter site www.oanda.com. 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'. Note that prices in the GDF price catalogueⁱⁱ can fluctuate during the year if, for example, a long-term agreement with different suppliers comes to an end. In addition, for certain manufacturers, GDF has provided so-called 'staircase prices', where price per unit varies depending on the quantities that are purchased.

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 and The Union 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 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

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/a>

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: J01GB06.⁸⁵
- Included in the WHO Guidelines as a Group 2 injectable agent.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ and in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- Presentations available: solution for injection: 500mg/2ml; 100mg/2ml. As powder for injection: 100mg, 500mg & 1g.
- First approved by US Food and Drug Administration (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 1981.⁸⁸
- 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).⁸⁹

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Cipla	Medochemie	Pharmathen Hellas	Pharmatex	GDF pooled procurement
Quality status	WHO PQ approved	SRA approved	WHO PQ approved	SRA approved	GDF Quality Assurance Policy
500mg/2ml solution for injection	2.060	0.750	No response received from manufacturer	0.741	0.805 (Pharmatex) 1.016–1.059 (Medochemie)* 1.950 (Cipla)

* These are the highest and lowest of a range of prices offered, depending on the quantities ordered.

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 amikacin.

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, with a second source (Pharmathen Hellas) being WHO-prequalified in April 2013. An additional two products are currently undergoing WHO prequalification; 1g/vial and 500mg/vial.

Suitability for use in developing country settings

Amikacin, like other aminoglycosides and capreomycin, cannot be administered orally. This imposes

burdens both on 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 this publication. There is at least one stringent regulatory authority-approved source available (e.g. Bristol-Myers Squibb). The product 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: J01GB04.⁸⁵
- Included in the WHO Guidelines as Group 2 injectable agent.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ and in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- Presentations available: solution for injection: 1g/4ml, 500mg/2ml, 1g/3ml. As powder for injection: 1g/vial.
- First approved by US Food and Drug Administration (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.⁹⁰

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	1.500	xx	0.800	0.826 (Panpharma)
1g/4ml solution for injection	xx	Manufacturer did not agree to publish prices	xx	2.580 (Meiji)

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 (in France). Meiji did not respond to questionnaires for the purpose of this publication and noted that all supply goes through GDF.

No sources of kanamycin are WHO-prequalified, although one manufacturer (Macleods) has submitted a dossier for WHO prequalification for the 500mg/vial formulation and has been accepted for evaluation. An additional source for 1g/vial is undergoing WHO prequalification.

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 has resolved issues with active pharmaceutical ingredient (API) production which had resulted in an interruption of supply to several national TB programmes in 2010, although the production only resumed in late 2011. Meiji was identified by GDF as an alternative

source in 2010; however their limited production capacity means the price of their product is considerably higher than Panpharma's.

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 active pharmaceutical ingredient (API) have been and still are 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. This imposes burdens both on 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, 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.

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: J01GB06.⁸⁵
- Included in the WHO Guidelines as a Group 2 injectable agent.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ and in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- Presentations available: 1g powder for injection.
- First approved by US Food and Drug Administration (FDA): 2 June 1971.⁹¹
- 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.⁹¹

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Akorn	Aspen	Macleods	Vianex	GDF pooled procurement
Quality status	SRA approved	Under evaluation by WHO PQ	Under evaluation by WHO PQ	SRA approved	GDF Quality Assurance Policy
1g powder for injection	6.250	9.065	5.000	5.850*	6.250 (Akorn) 5.557 (Vianex)

*MSF negotiated price; please contact the manufacturer for additional pricing information.

SPOTLIGHT ON ACCESS ISSUES

Capreomycin shows moderate cross-resistance to amikacin and kanamycin.

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

Number of quality sources

GDF have identified two quality-assured sources available for supply: Akorn – which had bought Eli Lilly's US licence; and, in 2011, Vianex – a manufacturer based in Greece, which has received stringent regulatory authority approval in Spain.

With only two quality-assured sources currently available for TB procurement, the supply of capreomycin is still considered vulnerable; however, five companies, including Macleods and Aspen, have submitted a dossier for WHO prequalification.

Active Pharmaceutical Ingredient

Issues with the production of the active pharmaceutical ingredient (API) have been and are still the main barrier in increasing the number of quality-assured sources for the finished product.

Capreomycin 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.

Eli Lilly transferred the technology for capreomycin API to only one manufacturer, Chinese generic producer Hisun, which received US FDA approval in 2006. As the majority of manufacturers are still using Hisun's API, access to capreomycin remains vulnerable, even as increasing numbers of sources of the finished product become available. It is therefore important to secure a second quality-assured API source.

Other API manufacturers exist, but have not been approved by a stringent regulatory authority or by the WHO Prequalification Programme.

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 certain volume had been ordered, and \$4.00 thereafter. The price at which countries can procure capreomycin has increased considerably since Eli Lilly stopped production, and instead transferred technology to other companies (Aspen, Hisun, and SIA International).

GDF currently procures the Akorn product at \$6.25 per vial. Vianex-sourced capreomycin is available for

GDF procurement at \$5.58 per vial. However, with a new quality-assured source identified and five suppliers set to receive WHO prequalification, it is anticipated the price will eventually decrease.

Suitability for use in developing country settings

Capreomycin, similarly to amikacin and kanamycin from the aminoglycosides class, cannot be administered orally. This imposes burdens both on 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.

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.



MOXIFLOXACIN (Mfx)

GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: J01MA14.⁸⁵
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.¹³
- Not included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ nor in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- Presentations available: 400mg tablet.
- First approved by US Food and Drug Administration (FDA): 12 October 1999.⁹²
- 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.⁹³

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Bayer	Cipla	Hetero	Macleods	Micro Labs	Sandoz	GDF pooled procurement
Quality status	SRA approved	WHO PQ approved	Under evaluation by WHO PQ (ERP approved till 30.11.2013)	WHO PQ approved	Under evaluation by WHO PQ	Under evaluation by WHO PQ (ERP approved till 31.5.2014)	GDF Quality Assurance Policy
400mg tablet	Manufacturer did not agree to publish prices	1.460	1.100	0.680	0.600	Manufacturer did not agree to publish prices	0.680 (Macleods) 1.200 (Hetero) 1.430 (Cipla)

SPOTLIGHT ON ACCESS ISSUES

Moxifloxacin use is increasing due to the emergence of MDR-TB and the key role that fluoroquinolones play in the treatment of drug-resistant forms of the disease. A major study is currently looking at a shortened first-line treatment regimen, including moxifloxacin. If this regimen is proven to be effective and is recommended for widespread adoption, the demand for moxifloxacin could significantly increase.

Based on 2011 WHO DR-TB programmatic guidelines, the use of later generation fluoroquinolones, such as moxifloxacin and levofloxacin, are preferred to ofloxacin. 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 a second source (Macleods) was prequalified. Currently four manufacturers are under

evaluation by WHO PQ, including Hetero and Micro Labs.

In the meantime, the Hetero and Sandoz products have received the GDF/Global Fund Expert Review Panel temporary approval for one year (until November 2013 and May 2014 respectively), making them eligible for procurement for Global Fund grants.

Sandoz did not provide a price for this publication but indicated that prices would depend on volumes.

With additional quality-assured sources entering the market, access to moxifloxacin appears to be relatively secure in the near future and prices, which in the past represented a barrier to access, are continuously decreasing.

Further sources of quality-assured moxifloxacin are also expected as other approved indications of use exist for the drug. Four generic manufacturers (Aurobindo, Dr Reddy's, Teva, and Torrent) currently have tentative US FDA approval, waiting to enter the US market when the patent expires in 2019.

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.

Evolution in price

Prior to the arrival of a quality-assured generic onto the market, the only option available was Bayer's product; prices for this source, as reported in the Global Fund Price and Quality Reporting (PQR) Tool, have ranged between US\$3.97 and \$5.03 per tablet in the last four years.

Since the arrival of a first and now a second quality-assured source on the market, prices have decreased considerably. In 2012, prices for procurement through GDF were between \$1.50 (Macleods) and \$1.68 (Cipla) per tablet; this year prices range between \$0.68 (Macleods) and \$1.43 (Cipla). The lowest unit prices for a quality-assured source of moxifloxacin has thus dropped by 60% in one year, allowing a considerable reduction in the cost of treatment regimens containing the drug.

As more generic manufacturers enter the market, it is expected the price will fall yet further.

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

Although the basic patent which covered the moxifloxacin molecule has now expired in most countries,⁵³ a subsequent patent claiming a crystal monohydrate form of moxifloxacin⁵⁴ blocks access to generic sources until 2016 in the countries where it has been granted. In addition, a patent on the tablet oral formulation⁵⁵ may prevent generic entry into the US market until 2019.

The following patents are listed by the US FDA for moxifloxacin 400mg tablet:⁵⁶

US patent number.	Expiry date
5607942	4 March 2014
5849752	5 December 2016
6610327	29 October 2019

In India, although the patent application on the crystal monohydrate form was rejected after a pre-grant opposition, additional patents on other pharmaceutical forms have been granted. However, these patents do not block generic production of the tablet formulation.

Similarly, 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, 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.

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 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 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 other 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 a class effect but is most pronounced with moxifloxacin.



LEVOFLOXACIN (Lfx)

GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone.
- ATC Code: J01MA12.⁸⁵
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ and in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷ 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 Food and Drug Administration (FDA): 20 December 1996. The paediatric formulation (25mg/ml oral solution) was approved on 21 October 2004.⁹⁴
- 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).⁹⁴

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Apotex	Cipla	Hetero	Macleods	Medochemie	Micro Labs	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	Under evaluation by WHO PQ (ERP expired on 31.6.2013)	Under evaluation by WHO PQ	SRA approved	WHO PQ approved	GDF Quality Assurance Policy
250mg tablet	0.090*	0.049	0.075	0.050	0.044	0.087	0.051 (Hetero) 0.048 (Cipla) 0.087 (Micro Labs)
500mg tablet	0.130*	0.077	0.140	0.070	0.076	0.163	0.074 (Hetero) 0.075 (Cipla) 0.163 (Micro Labs)
750mg tablet	0.150*	xx	xx	0.150	xx	xx	xx

* Incoterm 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 Micro Labs following in October 2012 and Apotex in June 2013. Currently an additional six manufacturers for the 250mg product and four manufacturers for 500mg (including Hetero and Macleods), are under evaluation by WHO Prequalification. A sizeable 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, and one more source (Macleods) is under evaluation by WHO PQ.

Evolution in price

The price of levofloxacin does not appear to be an issue, and it has continued to decrease over the last year.

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 of age, 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 of time 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 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.



OFLOXACIN (Ofx)

GROUP 3

GENERAL INFORMATION

- Therapeutic Class: Fluoroquinolone. in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- ATC Code: JJ01MA01.⁸⁵
- Included in the WHO Guidelines as a Group 3 Fluoroquinolone.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ and
- Presentations available: 200mg, 300mg, 400mg tablet.
- First approved by US Food and Drug Administration (FDA): 28 December 1990.⁹⁵
- Approved indication in the US: Ofloxacin is approved for the indications of acute bacterial exacerbations of chronic bronchitis, acute uncomplicated urethral and cervical gonorrhoea, non-gonococcal urethritis and cervicitis, acute pelvic inflammatory disease, and uncomplicated skin and skin structure infections.⁹⁵

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Cadila	Cipla	Macleods	Micro Labs	GDF pooled procurement
Quality status	Under evaluation by WHO PQ (ERP approved till 31.1.2014)	WHO PQ approved	WHO PQ approved	WHO PQ approved	GDF Quality Assurance Policy
200mg tablet	No response received from manufacturer	0.049	0.060	0.063	0.048 (Cipla) 0.060 (Macleods)
400mg tablet	No response received from manufacturer	0.090	xx	0.117	0.089 (Cipla) 0.119 (Micro Labs)

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

Today, three 200mg formulations (Cipla, Macleods, Micro Labs) and two 400mg formulations (Cipla and Micro Labs) have been prequalified by WHO. Macleods' 400mg formulation is still under evaluation by WHO PQ.

In addition, Cadila's 200mg and 400mg formulations have received joint GDF/Global Fund Expert Review Panel temporary approval (until January 2014), making them eligible for Global Fund procurement.

Approved indication

The 2011 WHO DR-TB programmatic guidelines recommend use of later generation fluoroquinolones. As with other

Group 3 drugs, ofloxacin does not have a TB indication approved by any stringent regulatory authority.

Paediatrics

The safety and efficacy of ofloxacin 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.

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 settings where DR-TB is prevalent.

HIV co-infection

No antiretroviral interaction studies have been performed, however one source suggests there may be a potential interaction with atazanavir and lopinavir.

Protease inhibitors and efavirenz may prolong QT interval, so caution is advised in concomitant use with ofloxacin, 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: J04AD03.⁸⁵
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicine⁸⁶ and in 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- Presentations available: 250mg tablet, 125mg tablet.
- First approved by US Food and Drug Administration (FDA): 30 April 1965.⁹⁶
- 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.⁹⁶

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Cipla	Lupin	Macleods		Micro Labs	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	WHO PQ approved	Under evaluation by ERP	WHO PQ approved	GDF Quality Assurance Policy
125mg tablet	xx	xx	xx	0.112	xx	xx
250mg tablet	0.077	Manufacturer did not agree to publish prices	0.128	xx	0.078	0.068 (Lupin) 0.075 (Cipla) 0.128 (Macleods)

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 that is currently under evaluation by the GDF/Global Fund Expert Review Panel.

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.

Currently there are no paediatric quality-assured formulations available (at the time of going to print the Macleods 125mg formulation has not received ERP approval). 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 settings where DR-TB is prevalent.

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: J04AD01.⁸⁵
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.¹³
- Not included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ nor in the 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- 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 process in Germany on 14 June 2005.⁹⁷
- 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.⁹⁸

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Cadila	Fatol	Micro Labs	Olainfarm	GDF pooled procurement
Quality status	Under evaluation by WHO PQ (ERP approved till 31.12.2013)	SRA approved	WHO PQ approved	SRA approved	GDF Quality Assurance Policy
250mg tablet	No response received from manufacturer	0.167	0.109	0.120	0.109 (Micro Labs) 0.155 (Fatol)

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, Micro Labs was the first manufacturer to secure WHO Prequalification approval for prothionamide, making it the third quality-assured source for the drug, given the two sources approved by stringent regulatory authorities (Germany's Fatol and Latvia's Olainfarm).

An additional two manufacturers have submitted their dossiers for WHO prequalification.

Cadila has received joint GDF/Global Fund Expert Review Panel temporary approval (running until the end of 2013), making it eligible for Global Fund procurement.

The increasing number of quality-assured sources of prothionamide is gradually improving its supply, and the price of prothionamide is expected to fall further.

Paediatrics

The safety and effectiveness of prothionamide 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.

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 settings where DR-TB is prevalent.

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.



CYCLOSERINE (Cs) GROUP 4

GENERAL INFORMATION

- Therapeutic Class: Analog of D-alanine.
- ATC Code: J04AB01.⁸⁵
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines⁸⁶ and in 4th edition of the WHO Model List of Essential Medicines for Children.⁸⁷
- Presentations available: 250mg capsule.
- First approved by US Food and Drug Administration (FDA): 29 June 1964.⁹⁹
- 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.⁹⁹

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Aspen	Biocom	Chao Center / Purdue	Cipla	Dong A	Lupin	Macleods	Micro Labs	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ approved	SRA approved	Under evaluation by WHO PQ (ERP approved until 31.12.2013)	WHO PQ approved	Under evaluation by WHO PQ (ERP approved until 30.6.2014)	WHO PQ approved	Under evaluation by WHO PQ	GDF Quality Assurance Policy
250mg capsule	0.781 (bottle)	No response received from manufacturer (bottle)	No response received from manufacturer (bottle)	Manufacturer did not agree to publish prices (bottle)	0.520 (blister)	Manufacturer did not agree to publish prices (blister)	0.430 (blister)	0.389 (blister)	0.408 (Lupin –blister)* 0.430 (Macleods –blister) 0.480 – 0.520 (Dong A –blister)**

*This price was provided by GDF and does not appear in the online catalogue.

** These are the highest and lowest of a range of prices offered, depending on the quantities ordered.

Note: GDF pooled procurement no longer lists bottle pricing.

SPOTLIGHT ON ACCESS ISSUES

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

Due to the hygroscopic characteristic of cycloserine, it is recommended to use the blister form in countries with high humidity and temperature.

Number of quality sources

Eli Lilly, the original licence holder of cycloserine, has 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, Aspen, Dong A, Macleods, and Biocom, the latter having secured approval in August 2013. In addition, Chao Center/Purdue have received approval from a stringent regulatory authority.

Cipla and Lupin and have received joint GDF/Global Fund Expert Review Panel temporary approval (until December 2013 and June 2014, respectively), making them eligible for Global Fund procurement.

Four other manufacturers, including Micro Labs and Lupin, 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. Another API manufacturer, Dong A, also exists.

Currently the majority of the manufacturers producing the blister form are using one API source. As a result, access to cycloserine remains vulnerable, even as increasing numbers of sources of the finished product become available.

Evolution in price

In the last year, with the arrival of two more quality-assured sources, prices have decreased from between US\$0.58 and 0.80 per unit, to between \$0.41 and 0.52 per unit. The lowest unit price for a quality-assured source of cycloserine has dropped by 26% in one year, which means a considerable fall in the cost of treatment regimens containing this drug.

Paediatrics

The British National Formulary provides doses for children aged two to 18, 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.

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 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: J04AK03.⁸⁵
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent.¹³
- No longer included in the current WHO Model Lists of Essential Medicines for Adult and Children.^{86, 87}
- 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 the posterior registration process in Germany. The filing date for this process was 1 January 1978.⁹⁸
- Approved indication in Germany: Treatment of tuberculosis in adults and adolescents aged 14 or older.⁹⁸

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Fatol	GDF pooled procurement
Quality status	SRA approved	GDF Quality Assurance Policy
250mg capsule	1.513	1.666 (Fatol)

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. Currently no manufacturers have 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, 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.

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 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: J04AA01; for PAS-sodium: J04AA02.⁸⁵
- Included in the WHO Guidelines PAS: as a Group 4 oral bacteriostatic second-line agent. PAS-sodium: not included.¹³
- PAS is included in the 18th edition of the WHO Model List of Essential Medicines and in the 4th edition of the WHO Model List of Essential Medicines for Children. PAS-sodium is not included in either document.^{86, 87}
- 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 Food and Drug Administration (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 1994.¹⁰⁰
- 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.¹⁰⁰

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	1.567	1.333 – 1.533* (Jacobus)

* These prices were provided by GDF and do not appear in the catalogue. These are the highest and lowest of a range of prices offered, depending on the quantities ordered.

PAS-SODIUM	Macleods	Olainfarm	GDF pooled procurement
Quality status	WHO PQ approved	WHO PQ and SRA approved	GDF Quality Assurance Policy
60% w/w granules – 9.2g sachet	1.300	xx	1.300 (Macleods)
60% w/w granules – 100g jar	14.250 (1.311 per 9.2g)	xx	14.250 (Macleods)
Powder for solution – 5.25g sachet	xx	1.520	1.370 (Olainfarm)

SPOTLIGHT ON ACCESS ISSUES

With moxifloxacin, capreomycin and cycloserine, PAS is one of the four 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), 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 a year, although the lowest price for a quality-assured source of PAS-sodium has dropped by 13.91%. Nevertheless the prices of both PAS and PAS-sodium remain a concern, and no additional quality-assured sources have been identified since 2011.

Suitability for use in developing country settings

With none of the quality-assured sources of either PAS or PAS-sodium presented in the same formulation

– the concentration of PAS varies between product and manufacturer – dosing can be particularly confusing if multiple formulations exist in one treatment programme.

The conversion is as follows: one 4g sachet of Jacobus's PAS = one 9.2g sachet of Macleods 60 % w/w PAS-sodium granules = one 5.52g sachet of Olainfarm PAS-sodium powder for solution.

In addition, the various formulations have different storage conditions, which can present issues for treatment programmes. While PAS-sodium products do not require any special storage conditions, PAS is required to be stored in a cold chain below 15°C. This is problematic for many settings where DR-TB is prevalent, as maintaining a functional cold chain requires a certain level of investment both in infrastructure and human resources. However, the latest PAS stability data states that PAS can be kept frozen and stored in conditions at 40°C and 75% humidity for one month without risk of degradation.

Paediatrics

The safety and effectiveness of PAS and PAS-sodium 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.

As there is no paediatric formulation available, paediatric doses are obtained by measuring the adult granular formulations. Jacobus supply a graduated dosage scoop for PAS, and Macleods offer 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: J04BA01.⁸⁵
- Included in the WHO Guidelines as a Group 5 medicine; agents with unclear efficacy.¹³
- Included in the 18th edition of the WHO Model List of Essential Medicines (as an anti-leprosy medicine)⁸⁶ and in the 4th edition of the WHO Model List of Essential Medicines for Children (as an anti-leprosy medicine).⁸⁷
- Presentations available: 50mg and 100mg soft-gel capsules.
- First approved by US Food and Drug Administration (FDA): 15 December 1986.¹⁰¹
- 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.¹⁰¹

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	
100mg soft-gel capsule	Manufacturer did not agree to publish prices	1.208 (Novartis via Pharmaworld)

SPOTLIGHT ON ACCESS ISSUES

Clofazimine is a Group 5 medicine which is mainly used in patients with pre-XDR-TB and XDR-TB, currently a very small market. With no official indication for DR-TB, and owing to its effectiveness having not clearly been established, it is not routinely used for DR-TB treatment. The 2011 WHO programmatic guidelines 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 (see introduction), and systematic reviews published in the last year and a half suggests that clofazimine could be considered as an additional therapeutic option in the treatment of DR-TB.¹⁰

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 leprosy,⁵⁷ Novartis did not submit a price for this publication.

As TB programmes' demand for this drug increased, WHO has since 2008 been in discussion with Novartis to address the liability for off-label use and patient safety of clofazimine for TB use, in order to make the drug available for MDR and XDR-TB treatment.

Five years on, the difficulties in accessing clofazimine for DR-TB treatment remain acute,⁵⁸ with no concrete plan having yet been disclosed by the company to increase production to meet TB needs, nor to transfer technology for the finished product formulation to another manufacturer. Novartis needs to ensure a secure affordable supply of clofazimine for the use in MDR-TB treatment or provide the necessary details for a tech transfer to allow another manufacturer to take over the supply of quality-assured clofazimine.

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, efforts to engage a second quality-assured source in order to ensure access to clofazimine for DR-TB have not been successful so far.

In order to send a clear message to manufacturers that clofazimine is needed, there was a call to include the drug in the WHO Prequalification Expression of Interest (EoI). This has yet to happen. Clofazimine is included however 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.⁵⁹

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

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

The GDF catalogue lists clofazimine 100mg, but not the 50mg strength. 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\$1.21 per 100mg and \$0.68 per 50mg capsule through Pharmaworld, a supplier in Switzerland.^{60, 61}

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.

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

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.



LINEZOLID (Lzd)

GROUP 5

GENERAL INFORMATION

- Therapeutic Class: Oxazolidinone antibiotic.
- ATC Code: J01XX08.⁸⁵
- Included in the WHO Guidelines as a Group 5 medicine; agents with unclear efficacy.¹³
- Not included in the current edition of the WHO Model Lists of Essential Medicines for Adult and Children.^{86, 87}
- Presentations available: 600mg tablet, 100mg/5ml powder for suspension.
- First approved by US Food and Drug Administration (FDA): 18 April 2000.¹⁰²
- 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.¹⁰³

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Hetero	Pfizer	GDF pooled procurement
Quality status	Under evaluation by SRA (ERP approved till 31.5.2014)	SRA approved	xx
600mg tablet	8.000	Manufacturer did not agree to publish prices	6.900 (Hetero)*
100mg/ml powder for suspension	xx	Manufacturer did not agree to publish prices	xx

* This price was provided by GDF and does not appear in the online catalogue.

SPOTLIGHT ON ACCESS ISSUES

Although linezolid has no official indication for DR-TB treatment, the 2011 WHO programmatic guidelines recommend the use of linezolid as a Group 5 drug for DR-TB.¹³ In April 2012, a systematic review outlined the efficacy of linezolid in DR-TB treatment. Data has also been presented at international conferences, and small case series reports have been published.⁶²

Linezolid has a relatively high number of adverse side effects, including myelosuppression, anaemia, and sometimes irreversible peripheral and optical neuropathies. Nonetheless, linezolid is a critical drug to have as an available option for treatment of patients with XDR-TB, and could be a promising candidate for inclusion in an improved MDR-TB regimen.

Number of quality sources

Currently, only one manufacturer – Pfizer – is approved by a stringent regulatory authority.

In May 2013, however, Hetero received temporary approval from the GDF/Global Fund Expert Review Panel (valid until the end of May 2014), meaning the Hetero product is now eligible for Global Fund procurement. In parallel, Hetero has also submitted a dossier for linezolid to the US FDA.

A further four manufacturers (Teva, Mylan, Glenmark and Gate Pharma)

have tentative approval from the US FDA. The basic patent on linezolid expires in the US in November 2014 – after this date, companies could produce quality-assured linezolid for the treatment of nosocomial infections in Europe and the US. If so, the increased availability of additional quality-assured sources will represent an opportunity to address more affordably the needs of DR-TB programmes for this product.

In order to send a clear message to manufacturers that linezolid

is needed for DR-TB treatment, and incentivise wider production, there was a call to include the drug in the WHO Prequalification Expression of Interest (EoI). This has yet to happen. Linezolid is included however 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.⁵⁹

Products from additional manufacturers exist in India, but it is unknown whether they comply with WHO quality standards.

Evolution in price

Due to patents covering linezolid in the US and a number of other countries, the cost of the drug is extremely high. Patients for whom conventional DR-TB treatment is failing but who could have a chance to survive through the use of linezolid are denied this option due to the prohibitively expensive cost of the drug.

In South Africa, for example, MSF pays ZAR676 (\$68)ⁱ per tablet for the price of Pfizer-produced linezolid through the private sector.⁶³ With treatment duration lasting four to six months, this makes the cost of linezolid alone \$8,000 – \$13,000 per patient, to which the cost of other medicines in the complete two-year regimen needs to be added.

The arrival of the first quality-assured generic linezolid, now eligible for Global Fund procurement through GDF, has changed matters somewhat. But the price of the drug remains very high, currently at \$8 per tablet. Last year, for the purpose of this publication, Hetero quoted a price of \$2.50 per tablet – and attributed the 300% price increase to higher manufacturing costs, owing to limited demand.

Securing a number of quality-assured generic sources will be critical to bringing down the price of linezolid. National TB programmes and international agencies must also forecast their demand for linezolid, and make estimates known to manufacturers in order to guarantee supply and secure lower prices.

Patents

The basic patent claiming linezolid was filed by Upjohn Companyⁱⁱ in the US in 1993 and will expire on 18 November 2014.⁶⁴ Upjohn Company also filed patents in the US on a crystalline form II⁶⁵ and on a tablet formulation in 2002;⁶⁶ these patents could impede generic competition in the US until 2021.

The following patents are listed by the US FDA for linezolid:⁶⁶

US patent number	Expiry date
5688792	18 November 2014
6514529	15 March 2021
6559305	29 January 2021

Four generic companies have already received Abbreviated New Drug Application (ANDA) approvals in the US, allowing them to manufacture linezolid once the patent barriers are removed. After Teva announced that it intended to launch its product, the company was sued by Pfizer in January 2010, with Pfizer alleging that Teva's plan was an infringement of its patents. In 2012, Pfizer successfully blocked the launch of Teva's generic version through a settlement between the parties.⁶⁷

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. The patent application on the crystalline form II was rejected. With no patent barriers preventing generic production, Hetero was able to manufacture a new source to compete with the Pfizer product.

But the patent status in other countries with high burdens of disease is not clear. The patent on the crystalline form II has been applied for or granted in many developing countries including Argentina, Brazil, China, Colombia, Mexico, and Ukraine. In South Africa, Pfizer managed to obtain two key patents on linezolid related to composition of matter⁶⁸ and crystalline form II.⁶⁹ The first patent on composition of matter will expire in 2014 while the patent on crystalline form II, though lapsed due to non-payment of renewal fees, is set to run until June 2022.⁷⁰ Patent barriers in South Africa are further complicated by Pfizer's product being unregistered for a TB indication, and the company subsequently failing to bid on government TB drug tenders requesting linezolid suppliers.⁷¹

Secondary patents, and in particular the patent on the crystalline form II may block generic competition even after the expiration of the basic compound in 2014. As with Teva in the US, Pfizer could use a threat of litigation to deter any efforts by Hetero to market its product.

But the patents do not necessarily block generic production altogether. Generic companies such as Hetero may be able to circumvent patent barriers and develop alternative formulations, provided they either develop a non-infringing form of linezolid or file for revocation of certain patents. Linezolid should, however, serve as an example to countries to enact and enforce stricter patentability criteria in national legislation, in order to prevent companies like Pfizer from extending their patent monopolies, and blocking access to life-saving medicines.

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.

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. The MSF projects in Khayelitsha, South Africa, and Mumbai, India for example, are using linezolid in DR-TB regimens for co-infected patients who are also on antiretrovirals. As of August 2013 in Khayelitsha, 78% of HIV-positive patients taking linezolid for one month or more (treatment duration range: 2–17 months) had culture-converted and remained culture negative – an early sign that treatment may be successful. 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.

i. Prices converted on www.oanda.com on 21 September, 2013

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



BEDAQUILINE (Bdq)

GENERAL INFORMATION

- Therapeutic Class: diarylquinoline (first-in-class) with bactericidal and sterilising activity against *Mycobacterium tuberculosis* or other mycobacterial species.⁷²
- ATC Code: J04AK05.⁷³
- WHO issued interim guidelines on the use of bedaquiline to treat MDR-TB in June 2013.⁷⁴
- Bedaquiline was not allocated a treatment group, but its use is similar to Group 5 drugs.
- Not included in the current WHO Model Lists of Essential Medicines for Adult and Children.
- Presentations available: 100mg uncoated tablet.
- First conditionally approved by US FDA: 28 December 2012.⁷⁵
- 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.⁷⁶

PRICE (IN US\$) AND QUALITY INFORMATION

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

	Janssen
Quality status	SRA approved*
100mg tablet	High-income countries: 159.574 Upper middle-income countries: 15.957 Least-developed/resource-limited countries: 4.787

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

SPOTLIGHT ON ACCESS ISSUES

Bedaquiline received accelerated approval by the US FDA in 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.

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.^{77, 74}

There are concerns around safety however. During drug trials, 10 out of 79 patients in the bedaquiline group died, compared to two 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 2013.⁷⁴

Number of quality sources

Janssen is currently responsible for all global manufacturing of bedaquiline. When in the future greater numbers of patients are reached worldwide, Janssen may look into engaging with other global partners.

Janssen has already submitted registration dossiers for bedaquiline in the EU and five additional countries (China, India, South Africa, Thailand, Vietnam). Registration in a further 15 countries is planned in the near future. 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. Pharmstandard has already submitted a registration dossier in Russia.

Outside the US, the drug can be accessed through compassionate use programmes (see introduction)—MSF for example is currently using bedaquiline under compassionate use in Armenia and intends to do so in Colombia and Swaziland. As of August 2013, 184 patients worldwide had received bedaquiline through a compassionate use framework since 2011.

In South Africa, registration of bedaquiline with the national regulatory authority, the Medicines Control Council (MCC), is still pending, but has been granted an accelerated review. A compassionate use programme treated four patients in South Africa in 2012, however this programme was later changed to a clinical access programme. In 2013, four sites, including the MSF project in Khayelitsha, started providing bedaquiline to patients with pre-XDR and XDR-TB through this programme, with additional sites added gradually across all provinces in South Africa. This offers a chance for patients with limited treatment options to access bedaquiline, though approval processes can be onerous in order to prevent uncontrolled widespread use while clinical trials are still ongoing. Only approved sites are eligible to prescribe bedaquiline, and doctors must apply to receive the drug through Janssen's compassionate use programme on a named-patient basis—a process which can take weeks, and delay the start of treatment. The drug's unusual administration schedule—daily for the first two weeks of treatment, and three times a week for the remaining six months—also requires additional training of staff. As of the end of August 2013, seven patients had been started on bedaquiline through the clinical access programme at the Khayelitsha site.

Prices

Janssen communicated for the purposes of this document 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'. 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.⁷⁸

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 Russia or China who are simultaneously high-burden TB countries and in the upper middle-income bracket.

In compassionate use programmes, Janssen provides bedaquiline free-of-charge.

Patents

Bedaquiline is a newly approved drug and comprehensive information on its patent status is not yet publicly available.

Patent searches show however that several patents have been filed by Janssen covering the basic compound, methods of use, formulation and preparation processes.

The patent which covers the basic compound (WO2004011436)⁷⁹ will not expire before July 2023. The basic patent has already been granted in several countries including Armenia, Azerbaijan, China, Kazakhstan, Russia, South Africa, Tajikistan, Ukraine and a number of African Regional Intellectual Property Organization (ARIPO) and Organisation Africaine de la Propriété Intellectuelle (OAPI) countries.⁸⁰

In India, the patent application on the basic compound (220/DELNP/2005) was filed by Janssen Pharmaceutica N.V. in January 2005, and granted (IN236811) in November 2009. The patent application on the salt form (1220/MUMNP/200) was also filed by Janssen Pharmaceutica N.V. in June 2009. A pre-grant opposition was filed against this application in March 2013 by the Network of Maharashtra People Living with HIV (NMP+). Other patent applications are still pending, including applications related to use of bedaquiline for treating drug-resistant Mycobacteria, to the use of bedaquiline for treating latent TB, and for processes.

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. This patent is pending in several countries and if granted it would not lapse before 2029.⁸¹

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 examination of patent applications and patent oppositions 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.

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. Paediatric studies are planned as part of the paediatric development plan required for the company to complete the regulatory approval process.

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.^{82, 83}

More detailed studies are required.

ANNEX 1: SUMMARY TABLE OF PRICES PROVIDED BY PHARMACEUTICAL COMPANIES

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

Prices listed with a # were provided directly by GDF and do not appear in the GDF online catalogue.

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	Cipla	Medochemie	Pharmathen Hellas	Pharmatex		
500mg/2ml solution for injection	0.805 (Pharmatex) 1.016 – 1.059 (Medochemie)* 1.950 (Cipla)	2.060	0.750	No response received from manufacturer	0.741		
KANAMYCIN		Macleods	Meiji	Panpharma			
1g powder for injection	0.826 (Panpharma)	1.500	xx	0.800			
1g/4ml solution for injection	2.580 (Meiji)		Manufacturer did not agree to publish prices				
CAPREOMYCIN		Akorn	Aspen	Macleods	Vianex		
1g powder for injection	6.250 (Akorn) 5.557 (Vianex)	6.250	9.065	5.000	5.850**		
MOXIFLOXACIN		Bayer	Cipla	Hetero	Macleods		
400mg tablet	0.680 (Macleods) 1.200 (Hetero) 1.430 (Cipla)	Manufacturer did not agree to publish prices	1.460	1.100	0.680		
LEVOFLOXACIN		Apotex	Cipla	Hetero	Macleods	Medochemie	Micro Labs
250mg tablet	0.051 (Hetero) 0.048 (Cipla) 0.087 (Micro Labs)	0.090***	0.049	0.075	0.050	0.044	0.087
500mg tablet	0.074 (Hetero) 0.075 (Cipla) 0.163 (Micro Labs)	0.130***	0.077	0.140	0.070	0.076	0.163
750mg tablet		0.150***			0.150		
OFLOXACIN		Cadila	Cipla	Macleods	Micro Labs		
200mg tablet	0.048 (Cipla) 0.060 (Macleods)	No response received from manufacturer	0.049	0.060	0.063		
400mg tablet	0.089 (Cipla) 0.119 (Micro Labs)		0.090	xx	0.117		
ETHIONAMIDE		Cipla	Lupin	Macleods	Micro Labs		
125mg tablet				0.112			
250mg tablet	0.068 (Lupin) 0.075 (Cipla) 0.128 (Macleods)	0.077	Manufacturer did not agree to publish prices	0.128	0.078		
PROTHIONAMIDE		Cadila	Fatol	Micro Labs	Olainfarm		
250mg tablet	0.109 (Micro Labs) 0.155 (Fatol)	No response received from manufacturer	0.167	0.109	0.120		

Drug	GDF pooled procurement	Companies			
CYCLOSERINE	GDF	Dong A	Lupin	Macleods	Micro Labs
250mg capsule (blister)	0.408* (Lupin) 0.430 (Macleods) 0.480-0.520* (Dong A)	0.520	Manufacturer did not agree to publish prices	0.430	0.389
		Aspen	Biocom	Chao Center/Purdue	Cipla
250mg capsule (bottle)	Not listed in the catalogue	0.781	No response received from manufacturer	No response received from manufacturer	Manufacturer did not agree to publish prices
TERIZIDONE		Fatol			
250mg capsule	1.666 (Fatol)	1.513			
PAS		Jacobus			
4g sachet	1.333–1.533** (Jacobus)	1.567			
PAS-SODIUM		Macleods	Olainfarm		
60% w/w granules – 9.2g sachet	1.300 (Macleods)	1.300			
60% w/w granules – 100g jar	14.250 (Macleods)	14.250 (1.311 per 9.2gr)			
Powder for oral solution – 5.25g sachet	1.370 (Olainfarm)		1.520		
CLOFAZIMINE		Novartis			
50mg soft-gel capsule		Manufacturer did not agree to publish prices			
100mg soft-gel capsule	1.208 (Novartis via Pharmaworld)	Manufacturer did not agree to publish prices			
LINEZOLID		Hetero	Pfizer		
600mg tablet	6.900 (Hetero)*	8.000	Manufacturer did not agree to publish prices		
BEDAQUILINE		Janssen			
100mg tablet	Not listed in the catalogue	High-income countries: 159.574 Upper middle-income countries: 15.957 Least-developed/resource-limited countries: 4.787			

* These are the highest and lowest of a range of prices offered, depending on the quantities ordered.

** MSF negotiated price; please contact manufacturer for additional pricing information

*** 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 were those quoted by companies.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
AKORN	No restrictions	No restrictions	Akorn is the sole US manufacturer for Capreomycin 1g powder for injection and is FDA approved in the United States. Akorn has the capacity to produce approximately 2 million units annually	Ex works
APOTEX	No restrictions	No restrictions		CIF by air to airport of destination
ASPEN	Excludes China, EU countries, India, Japan, Russia and USA	Excludes China, EU countries, India, Japan, Russia and USA		Ex works
BAYER	Not applicable; Bayer's moxifloxacin is not yet registered for treatment of TB	Not applicable; Bayer's moxifloxacin is not yet registered for treatment of TB	Not applicable; Bayer's moxifloxacin is not yet registered for treatment of TB	Not applicable; Bayer's moxifloxacin is not yet registered for treatment of TB
BIOCOM	No restrictions	No restrictions		Ex works
CIPLA	Generic-accessible countries	Public sector		Ex works
DONG A	No restrictions	No restrictions		Ex works
FATOL	No restrictions	No restrictions		Ex works
HETERO	No restrictions	No restrictions		Ex works
JACOBUS	No restrictions if purchased via MSF/GDF/GLC/Government	No restrictions if purchased via MSF/GDF/GLC/Government		Shipping and handling are billed at actual cost to the customer
LUPIN	No restrictions	No restrictions		Ex works
MACLEODS	Excludes Australia, Brazil, Canada, EU, Japan, New Zealand, Singapore, South Africa, South Korea, USA	No restrictions	Pricing is based on the volumes given by GDF in their tender; for smaller volumes, prices may be higher	Ex works
MEDOCHEMIE	No restrictions	No restrictions		
MICRO LABS	No restrictions	No restrictions		Ex works
OLAINFARM	No restrictions	No restrictions		Ex works
PANPHARMA	No restrictions	No restrictions	Forecast required in order to plan the API order	Ex works
PHARMATEX	No restrictions	Prices valid for MSF, Red Cross	30 days from the date of invoice	Ex works
SANDOZ INDIA	No restrictions	No restrictions		
VIANEX	No restrictions	Prices valid for MSF		

For more information on incoterms, 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.

Akorn

www.akorn.com

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GLOSSARY

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.

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.

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 a national legislation which establish under which condition 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).

Culture-converted: a person whose last two clinical samples are no longer growing *M. tuberculosis*, implying that bacteria are no longer present.

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 risk/benefit associated with the use of antiretroviral, anti-TB and antimalarial products which are not yet WHO-prequalified or authorised by a stringent regulatory authority. ERP will make recommendation to the Global Fund and the Global Drug Facility whether procurement of such products can be authorised. The recommendation shall be valid for a period of no more than 12 months or until the product is either WHO-prequalified or SRA-authorised. (<http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/>).

Extemporaneous preparation: Medicines prescribed by a physician and compounded by a pharmacist to fit the unique need of a patient in the absence of a commercially available, authorised, age-appropriate dosage or form of a medicine. They are a mixture of a commercially available active pharmaceutical ingredient or finished product with an appropriate vehicle(s).

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 is most commonly the lymph nodes, bones, central nervous system, cardiovascular and gastrointestinal systems.

FCA: “Free Carrier”. A commercial term (incoterm 2010) meaning that the seller hands over the goods, cleared for export, into the disposal of the first carrier (named by the buyer) at the named place. The seller pays for carriage to the named point of delivery, and risk passes when the goods are handed over to the first carrier.

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.

FOB: ‘Free on board’. A commercial term (incoterm 2010) meaning that the seller delivers when the goods pass the ship’s rail at the named port of shipment. This means that the buyer has to bear all costs and risks of loss or damage to the goods from that point. The FOB term requires the seller to clear the goods for export.

Global Drug Facility (GDF): A mechanism hosted by WHO 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. 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 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 the world's money to save lives. It invests in 150 countries to support large-scale prevention, treatment and care programs against the three diseases and it channels 82 percent of the international financing for TB.

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 can provide treatment for people with multidrug-resistant tuberculosis in line with the WHO guidelines, the latest scientific evidence and country experiences. The Initiative consisted of a secretariat, the Green Light Committee (an expert review and WHO advisory body) and the Global Drug Facility (the drug procurement arm of the Initiative). Since 2011, there is no need anymore to get GLC approval to procure quality-assured second line TB drugs through GDF. GLC has been also 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 will be 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 FDA's 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, which 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.

Pharmacodynamic (PD): Branch of pharmacology, which 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 the first-line drugs are no longer effective to cure a patient. In the case of tuberculosis, they are less effective and have many more side-effects than first-line drugs. This report looks at the sources and prices of second-line anti-tuberculosis medicines classified in World Health Organization Groups 2 (injectable agents), 3 (fluoroquinolones), 4 (oral bacteriostatic second-line agents) and 5 (agents with unclear efficacy), as well as new drugs like bedaquiline.

Staircase pricing: Global Drug Facility prices occasionally depend 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 World Health Organization (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: Is 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. It is now widely by the media. The term "totally drug-resistant" tuberculosis is not recognised by the WHO, after they held a meeting in 2012 to discuss the term. These cases are defined as extensively drug-resistant tuberculosis (XDR-TB), according to WHO definitions.

WHO Prequalification (PQ) Programme:

The Prequalification Programme, set up in 2001, is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. 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 suffering from extensively drug-resistant TB or XDR-TB.



ABBREVIATIONS

ANDA – Abbreviated New Drug Application

API – Active pharmaceutical ingredient

API PQ – Active Pharmaceutical Ingredient-Prequalification

ARIPO – African Regional Intellectual Property Organization

ATC - Anatomical Therapeutic Chemical

BfArM – Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)

BRICS – Brazil, Russia, India, China and South Africa

CEWG – Consultative Expert Working Group

CIF – Cost, insurance and freight

DR-TB – Drug-resistant tuberculosis

DS-TB – Drug-sensitive tuberculosis

EBA – Early Bactericidal Activity

EMA – European Medicines Agency

EoI – WHO Prequalification Expression of Interest

ERP – Expert Review Panel

EU – European Union

GLI – Global Laboratory Initiative

GDF – Global Drug Facility

GFATM – Global Fund to Fight AIDS, Tuberculosis, and Malaria

GLC – Green Light Committee

HIV – Human immunodeficiency virus

LIC – Low-income countries

MDR-TB – Multidrug-resistant tuberculosis

MCC - Medicines Control Council (South Africa)

MIC – Middle-income countries

MRC – Medical Research Council (UK)

MSF – Médecins Sans Frontières

NDA – New Drug Application

NGO – Non-governmental organisation

OAPI – Organisation Africaine de la Propriété Intellectuelle

PAS – Para-aminosalicylic acid

PDR-TB – Polydrug-resistant tuberculosis

PQ – Prequalification

R&D – research and development

SRA – Stringent regulatory authority

TAC – Treatment Action Campaign

TB – Tuberculosis

TDR-TB – Totally drug-resistant tuberculosis

TRIPS – Trade-Related Aspects of Intellectual Property Rights (Agreement)

USAID – US Agency for International Development

US FDA – US Food and Drug Administration

WHO – World Health Organization

WHO PQ – World Health Organization Prequalification Programme

w/w – weight for weight

XDR-TB – Extensively drug-resistant tuberculosis

ZAR – South African rand

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DISCLAIMER:

DR-TB Drugs Under the Microscope - The Sources and Prices of Medicines for Drug-Resistant Tuberculosis is a pricing guide and cannot be regarded as a company price list nor as a clinical guideline. It is crucial that any purchaser verify prices and availability as well as quality status directly with the supplier before procurement. Médecins Sans Frontières (MSF) or The Union have made every effort to ensure the accuracy of prices and other information presented in this report, but MSF or The Union make no representations or warranties, either expressed or implied, as to their accuracy, completeness or fitness for a particular purpose. Inclusion of a product in this document does not indicate MSF or The Union purchases or uses the product. Information in this guide is indicative only and not exhaustive, and should be verified with relevant offices when used for other than reasons of general information. Clinical decisions should not be made based on this document.



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