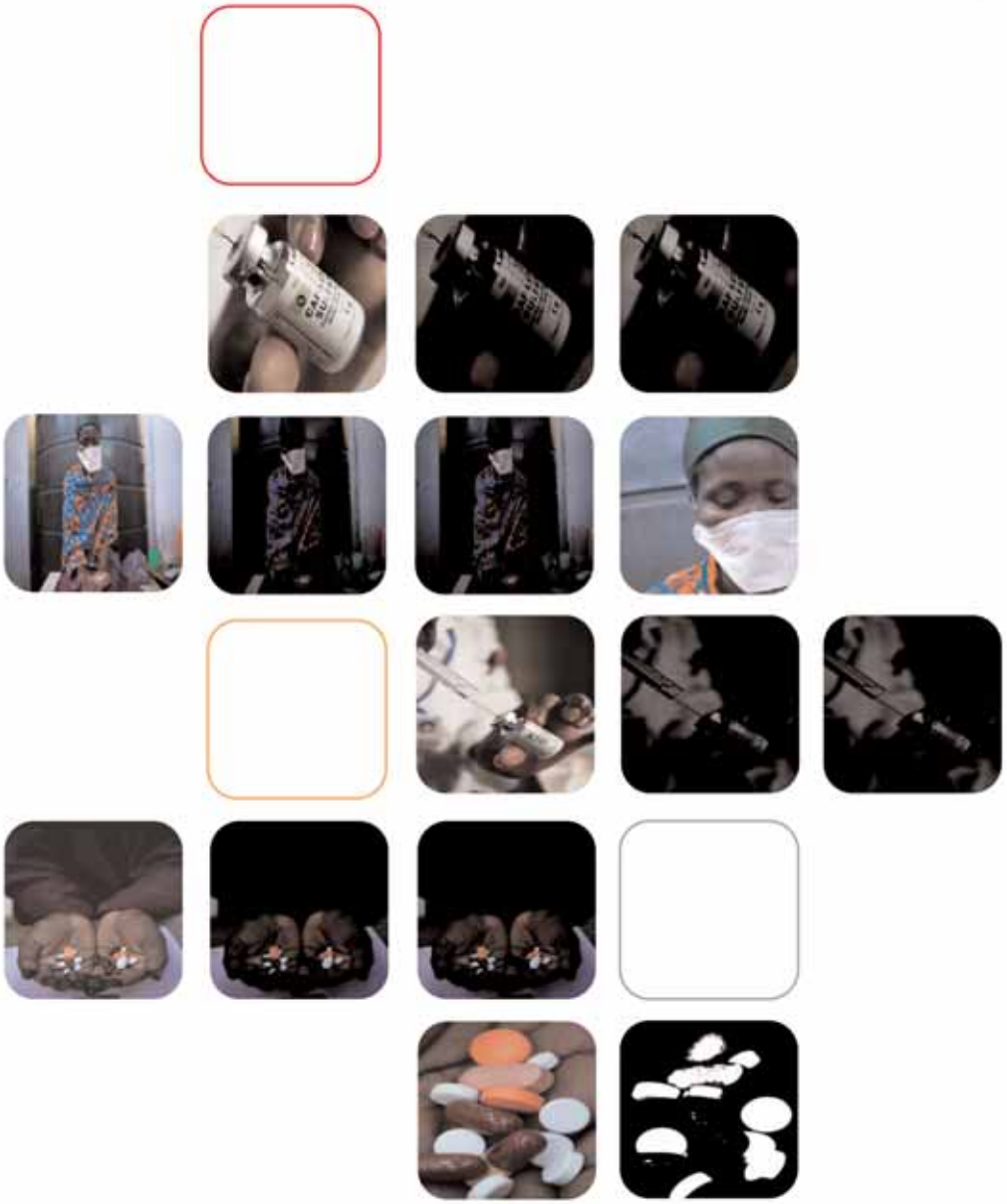
DR-TB drugs under the microscope



SOURCES AND PRICES for drug-resistant tuberculosis medicines

International Union Against Tuberculosis and Lung Disease

MEDECINS SANS FRONTIERES

THE MSF CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

In 1999, in the wake of Médecins Sans Frontières (MSF) being awarded the Nobel Peace Prize, MSF launched the Campaign for Access to Essential Medicines. Its sole purpose has been to push for access to, and the development of life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.

THE INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE

The mission of the International Union Against Tuberculosis and Lung Disease (The Union) is to bring innovation, expertise, solutions and support to address health challenges in low- and middle-income populations. With nearly 10,000 members and subscribers from 152 countries, The Union has its headquarters in Paris and offices serving the Africa, Asia Pacific, Europe, Latin America, Middle East, North America and South-East Asia regions. Its scientific departments focus on tuberculosis and HIV, lung health and non-communicable diseases, tobacco control and research.

March 2011

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Introduction

Tuberculosis (TB) is a curable disease that continues to kill nearly 1.4 million people[1] across the globe each year, and is the main cause of death in people living with HIV/AIDS[2]. Of the 9.4 million new tuberculosis cases each year, 440,000 are forms of the disease that are multi-drug-resistant[3], meaning they can not be treated with the two primary antibiotics used to treat TB. Over the last decade, roughly five million people developed drug-resistant TB, but less than 1% had access to appropriate treatment, and 1.5 million died[4].

That such an appallingly low proportion of patients should access appropriate treatment is due to a number of factors. Treating DR-TB is complicated from a programmatic perspective: treatment is individualised, tailored according to which drugs a patient is resistant to. It is long and taxing, requiring people to take a course of antibiotics for up to two years and endure often intolerable side effects. Partly as a result of the complexities of treatment, programmes must devote considerable resources to adherence counselling, the management of side effects and psychosocial care, all of which place large demands on human resources. In some countries, the lack of political will to appropriately address DR-TB is a major barrier.

Another factor that hampers scale-up of treatment - and the focus of this report - is the limited availability and high cost of quality-assured second-line medicines. For many DR-TB medicines, the sustainability of drug supply is constantly under threat and therefore extremely vulnerable to disruption. For some medicines, there is only one quality-assured source, while for others there may be several but they all rely on a single source of the active pharmaceutical ingredient required to make the drug.

Some of the DR-TB drugs come at extremely high prices, with the result that one patient's treatment can cost almost $9,000 - nearly 475 times more than a $19 treatment course for drug-sensitive TB. Alarmingly, in recent years prices have actually been increasing as some manufacturers put an end to subsidies that have kept prices lower.

DR, MDR, XDR, PDR: the many faces of resistant TB

Drug-resistant tuberculosis (DR-TB) is used to describe strains of TB that show resistance to one or more first-line drugs. 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).

All forms of resistance to more than one of the first-line antibiotics, and which are neither MDR-TB nor XDR-TB, are defined as polydrug-resistant TB (PDR-TB).

THE UNION AND TB

The International Union Against Tuberculosis and Lung Disease (The Union) has been the leading international TB control and prevention agency since 1920. Each year The Union works in more than 70 countries, providing technical assistance at the request of national tuberculosis control programmes; conducting operational research and clinical trials; organising conferences and courses; and publishing both a peer-reviewed journal and a range of technical guides. In addition, The Union regularly monitors MDR-TB project sites and provides technical assistance on all aspects of MDR-TB management in Africa, Asia, Latin America and the Middle East. Its clinical trial of a shortened standardised MDR-TB treatment regimen will begin enrolling patients in 2011 and has the potential to revolutionise the management of MDR-TB.

MSF AND TB

In 2010, MSF treated close to 30,000 people for tuberculosis, of which 3,300 were children under the age of 15. MSF - often working alongside national health authorities - treats patients for TB in 29 countries in a wide variety of settings, ranging from urban slums to rural areas, prisons or refugee camps.

In recent years, MSF has worked to increase the numbers of people it treats with drug-resistant tuberculosis from 11 patients in 2001 to around 1,000 people across 15 countries in 2010.

"Was it possible that I could live?" - The story of Happiness

DR-TB can be cured, but treatment requires people to take a course of up to six different antibiotics – as many as 20 pills per day for up to two years, plus, for the first six months, a daily painful injection. Patients often endure intolerable side effects. These can include nausea, severe vomiting, depression, aggressive behaviour, hallucinations, vertigo, hearing loss, diarrhoea and lethargy. Patients may need to take additional medication to mitigate these side effects. Treatment needs to be tailored to the precise drugs that will be effective for a patient, depending on their drug-resistance profile. People's lives are interrupted by DR-TB treatment, and many find adhering to it too arduous to bear. Happiness Dlamini from Swaziland shares what life is like on DR-TB treatment.

Photo © Krisanne Johnson

Happiness Dlamini lies with her daughter Nokwenza outside her home in Swaziland. She keeps her distance so she does not spread MDR-TB to her child.

Happiness Dlamini lives with her eleven year-old son and four-year old daughter in the village of Emhlabeni - four hours drive from Mbabane, the capital of Swaziland. Before getting sick, she worked as a housekeeper. She is living with HIV and is also infected with multidrug-resistant tuberculosis, which is all too common in the small southern African country. One third of those newly diagnosed with TB in Swaziland have DR-TB[12].

"I had been coughing for a long time, so after discussion with my family, we felt I should go get tested for TB," she says. "I was very scared when they told me I had MDR-TB. To me, it meant the end of my life, because everyone in my community that I knew had MDR-TB had died."

Happiness learned that if she was able to stick to her treatment, she had a good chance at surviving MDR-TB. She started treatment through MSF's community care MDR-TB programme in Shiselweni Region, after she was diagnosed in December 2010. When she started treatment, she had to take 18 and a half tablets every day, in addition to receiving a painful injection from a health worker who comes to her home. Now, over three months later her daily routine still consists of an injection and 15 and a half pills.

The side-effects the medicines cause are harsh - she can barely list all of them - and have made her feel mentally unstable and physically ill.

"It was like I was losing my mind - I had hallucinations and found myself banging against things at night," she says. "I have sore feet and my legs cramp up. I have diarrhoea and I often vomit after taking the pills, so I have to take them again if it was within 30 minutes to make sure I'm not defaulting on my treatment."

Every day, Happiness struggles not only with the burdens of treatment, but with the stress of not being able to provide for her family. And keeping her distance from her children to make sure they don't get infected is affecting her relationship with her four-year-old daughter in particular - little Nokwenza has now become closer to her grandmother.

Happiness has responded well to treatment so far and has been determined to stay the course. But she does not find it easy to be optimistic.

"I have to be honest that when it comes to my future, I am very unsure," Happiness says. "I really don't know what will happen."

The problems that plague DR-TB medicines

This report provides an overview of available DR-TB medicines, providing relevant information for each product, including its sources, quality status and price, that can aid treatment providers, treatment programmes and national procurement centres in making procurement decisions. Transparency of price and quality information is one problem that this document also aims to help overcome. In providing this overview, a number of important problems that hamper access to medicines are brought to light.

The medicines examined in this report are those DR-TB drugs classified in groups 2-5 of the World Health Organization's 2008 Guidelines for the Programmatic Management of Drug-resistant Tuberculosis. Certain problems are more relevant to some drug classes than others.

GROUPING	DRUGS
Group 1 - First-line oral agents	isoniazid*, rifampicin*, ethambutol*, pyrazinamide*, rifabutin*
Group 2 - Injectable agents	kanamycin, amikacin, capreomycin, streptomycin*
Group 3 - Fluoroquinolones	moxifloxacin, levofloxacin, ofloxacin
Group 4 - Oral bacteriostatic second-line agents	ethionamide, prothionamide, cycloserine, terizidone, p-aminosalicylic acid (PAS)
Group 5 - Agents with unclear efficacy	clofazimine, linezolid, amoxicillin/clavulanate*, thioacetazone*, imipenem/cilastatin*, high-dose isoniazid*, clarithromycin*

* this report does not include first-line oral agents, first-line injectable agents, or certain group 5 agents

How countries procure DR-TB drugs

In response to a growing need for DR-TB treatment - and to prevent further drug resistance from developing through improper use of DR-TB drugs - the World Health Organization, together with MSF, and other partners, created the 'Green Light Committee' Initiative (GLC) in 2000[9]. The core function of the Green Light Committee has been to provide technical review of proposed DR-TB treatment projects, and 'green-light' them if they meet certain criteria. Approved projects then get access to quality-assured drugs at reduced prices - since 2002, these have been procured through the WHO-hosted Global Drug Facility.

From 2000 to end 2010, a cumulative total of 105,140 patients were approved for treatment through the GLC - although less than half of these (under 30,000 patients) had actually been started on treatment by the end of 2009[72].

Until now, programmes without GLC approval are not allowed to turn to the Global Drug Facility to access WHO quality-assured medicines.

Not surprisingly, nearly one decade on, only 13% of the estimated DR-TB drug market is channelled through the Global Drug Facility. In 2010, only 12,000 patients were enrolled in GLC-approved treatment programmes, compared to an estimated 440,000 new cases and 150,000 deaths[3].

Many programmes continue to use DR-TB drugs from outside the GLC process, where drug quality may be uncertain, and drug prices may be substantially higher[7]. This is especially concerning in countries with the highest disease burden.

The GLC Initiative has been undergoing a reform process since early 2010 and an intended key change is to let all programmes purchase quality-assured medicines through the GDF[13].

Global DR-TB drug market

The global DR-TB market was estimated to be worth $300 million in 2010, with only $125 million procured through the public sector. Of this, only $40 million was channelled through the Global Drug Facility.

The market has been growing by approximately 5% per year, with India and China taking the largest share, at 63% and 17%, respectively[17].

1. Limited number of quality sources

Relatively few products for the treatment of drug-resistant tuberculosis are included on the WHO List of Prequalified Medicinal Products or approved by a stringent drug regulatory authority such as the US Food and Drugs Administration. Such quality approval is a requirement by donors financing MDR programmes such as the Global Fund to Fight AIDS, TB and Malaria.

To date, of the DR-TB medicines covered in this report, only six products (for five different drugs) have been prequalified by WHO and only four sources (for two different medicines) are recommended for purchase in 2011 by the Expert Review Panel[14], a joint mechanism of the Global Fund to Fight AIDS, TB, and Malaria and the GDF that gives temporary purchase permission for drugs still under evaluation.

Few quality-assured sources exist. For many DR-TB drugs, such as capreomycin, prothionamide, terizidone, PAS and clofazimine, only one quality-assured source exists. For others, including ethionamide*, moxifloxacin and PAS-Sodium, there are only two quality-assured sources. Although there has been some recent progress - with a decrease in the number of products that had only one supplier, down from 11 in 2008 to four in 2011[5] - for all of these medicines, supply is extremely vulnerable to disruption.

The example of kanamycin illustrates the risks associated with relying on few sources for a given medicine. In the past, several manufacturers had kanamycin registered for use in the US, although all but one subsequently ceased production, because of falling demand in wealthy countries. Today, only three quality-assured sources are identified. Of those, the first was forced to suspend production because of the relocation of its supplier of active pharmaceutical ingredient in 2009. The second also experienced a supply problem in 2010 and ceased production for a period of time, leaving programmes dependent on a third manufacturer with limited capacity, so much so that its production is solely dedicated to GDF procurement, leaving other DR-TB treatment programmes with no quality-assured source.

For a number of DR-TB medicines, multiple producers in Russia, India, China and other countries are known to manufacture DR-TB drugs, but whether they could comply with WHO or stringent regulatory authority standards is unknown. Part of the problem of too few quality-assured sources for international supply could be resolved by encouraging manufacturers to improve their compliance with internationally recognised quality standards and submit product dossiers for quality assessment through the WHO Prequalification Programme or stringent regulatory authorities.

One welcome step is that the Global Drug Facility now has a clear policy, sending a signal to manufacturers to invest in quality, by requiring products to be either quality assured by the World Health Organization's prequalification programme, or approved by the Expert Review Panel. The Panel provides time-limited approval for products that have fewer than three sources approved by either the WHO Prequalification or a stringent regulatory authority. With the implementation of the GDF quality-assurance policy, price is no longer the main determinant for purchasing decisions.

Sources of active pharmaceutical ingredients are limited. The difficulties faced in trying to increase the number of quality-assured sources for some DR-TB drugs are to a large extent due to those associated with the production of the active pharmaceutical ingredient (API). For several drugs, such as capreomycin and kanamycin, only one quality-assured API source has been identified. In the case of capreomycin, all quality-assured finished products identified in this document are reliant on a single source of API, again making the entire supply of capreomycin extremely vulnerable to disruption. A recent study for the GDF noted that the supply of API was vulnerable for amikacin, kanamycin, prothionamide and clofazimine[11].

Part of the problem is due to the complexity of production. For

* not including the temporary approval by ERP of Cipla's 250mg tablet of ethionamide.

example, producing the API for the injectables capreomycin and kanamycin requires a fermentation process that is more complex than the synthetic process. The complexity is further increased as the API should be sterile.

Some medicines that are active against DR-TB are not reaching the DR-TB market. Developed for the treatment of infectious diseases, some medicines do not have an approved indication for use in DR-TB, even though they have shown efficacy in in-vitro studies and have been used for many patients and recommended in treatment guidelines. This is particularly the case for the latest group of antibiotics used in DR-TB treatment, the fluoroquinolones (such as moxifloxacin, levofloxacin and ofloxacin).

Although a number of quality-assured manufacturers exist for such medicines - in the case of levofloxacin, for example, there are 13 producers that have secured tentative approval in the US, for moxifloxacin there are two and for ofloxacin three - none of them have applied to participate in the GDF procurement tender. As such, the perspective of higher earnings by targeting more profitable diseases than DR-TB acts as a barrier to increasing the number of quality-assured sources of DR-TB medicines.

Photo © Bruno de Cock

Getting medicines into countries: Lead times and regulatory constraints

There are additional barriers faced by treatment providers to getting drugs in countries. One is lead times. GDF is committed to deliver medicines within 90 days[15] after order confirmation. However, this commitment is sometimes difficult to respect due to long lead time or difficulty of production at manufacturer level. The GDF has thus decided to put in place a stockpile of DR-TB medicines, with support from UNITAID[16].

Delays in drug delivery are also largely due to national regulations, and regulatory issues form a barrier to accessing DR-TB drugs. As they are typically not registered in countries where treatment projects are located, MSF experience suggests that often cumbersome special authorisation is needed to import DR-TB medicines.

For manufacturers of some products that do not have an approved indication for TB, like fluoroquinolones, registration can be difficult. When these products are used as a part of a DR-TB treatment regimen, they are essentially being used “off label” for this indication. This may increase difficulties for manufacturers trying to register their products for the indication of TB in some countries.

Countries should use fast-track registration procedures to facilitate the importation if medicines are quality-assured by WHO or another stringent drug regulatory authority.

2. Limited affordability

First-line TB treatment costs $19 per patient for a six-month treatment course[32]. Yet the cost of DR-TB treatment is considerably more expensive, and this acts as a barrier to treatment scale up. For both drug-sensitive and drug-resistant TB, to the price of the medicines must be added significant costs in terms of biological monitoring, human resources for medical and psychosocial care, and treatment to counter side effects.

The price of DR-TB treatment varies considerably, as treatment must be individualised according to a patient's drug resistance profile. Drugs procured through the GLC/GDF cost between $4,400 and almost $9,000 per patient for a standard 18-24 month treatment course. For drugs purchased outside of the GLC/GDF, prices may be even higher.

These prices are a reflection of insufficient market competition among multiple producers, both at the level of API production, as well as at finished product level. They are also a consequence of limited demand for DR-TB drugs, as with low volumes, manufacturers cannot hope to achieve economies of scale necessary to bring prices down. This is one area where a new diagnostic test, by diagnosing patients more effectively and more quickly with DR-TB, will increase demand for more second-line anti-tuberculosis medicines.

The price of four medicines in particular weigh heavily in the overall cost of a DR-TB regimen. Overall costs of the DR-TB regimen are particularly driven by capreomycin, moxifloxacin, PAS and cycloserine.

For most DR-TB drugs, patents are not typically a factor in causing high prices because the medicines were developed so long ago that patents on most have long run out.

However, moxifloxacin is one notable exception. Until now, Bayer's monopoly has kept prices high. But now that there is one WHO Prequalified generic moxifloxacin source available, the situation will change, and as the number of generic sources increases, the price should fall. Although patents claiming moxifloxacin as a compound should have expired in most countries, subsequent patents could possibly stand in the way of generic production and/or distribution in countries where such patents have been granted and remain valid.

The threat of rising prices still exists for off-patent DR-TB drugs if producing countries introduce additional monopoly protection such as data exclusivity provisions, as for example currently demanded by the European Union as a part of the EU-India Free Trade Agreement negotiations.

Some DR-TB drug prices have increased considerably between 2001 and 2011, including for the medicines procured through the GDF for GLC-approved treatment programmes. The prices of amikacin, kanamycin, cycloserine and capreomycin have all increased substantially in recent years (see table below).

For kanamycin, the hike in price is partly due to GDF turning to Meiji after supply problems affected the production of more affordable versions made by APPPharma and PanPharma. For capreomycin and cycloserine, the rise in price can be explained by the fact that Eli Lilly has ceased production, and put an end to the subsidised prices it was offering the GLC. Since 2003, the US company has been actively engaged in technology transfer to generic manufacturers, and those who now produce charge substantially higher prices. In fact, the price of capreomycin is expected to continue rising, and double in the near future - from $4 to $8 per unit - as Eli Lilly's existing stock at the GDF eventually

Prices available for GLC - approved programmes, in US$

Products	July 2001	March 2011 (lowest price)	% Difference 2001/2011
Amikacin 500mg	0.11	1.20	+991%
Kanamycin 1g	0.36	2.58	+617%
Cycloserine 250mg	0.14	0.59	+321%
Capreomycin 1gr	1.02	4.00	+292%
Ethionamide 250mg	0.10	0.09	Stable
Prothionamide 250mg	0.10	0.10	Stable
PAS 4g sachet	1.51	1.57	Stable

runs out and Akorn's product is used. The impact on the overall cost of a DR-TB regimen is estimated to be around $720.

Prices directly from manufacturers - the overwhelming majority of patients who receive DR-TB treatment are not funnelled through the GLC process. They may receive treatment through national programmes or NGOs or other treatment providers, or more concerning is on the private market. No analysis of the private market was undertaken and is outside the scope of this report.

Photo © Dieter Telemans

MDR-TB patients in Cambodia.

3. The neglect of children and people living with HIV/AIDS

Until today, there has been very little research to even determine the best use of existing drugs used for MDR-TB. In fact, today's treatment for DR-TB is largely based on experience and expert opinion, not randomised clinical trials, with a large number of 'grey areas' where expert opinions may be conflicting[4].

Children are particularly neglected. At least 10-15% of total TB cases each year occur in children and a similar percentage can be assumed among new DR-TB cases in children[48]. Yet only two medicines featured in this report (amikacin and levofloxacin) have been developed as paediatric formulations, and these are not widely available. This means that 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 or 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. Only three medicines in this report have been licensed for use in children. One of those that is licensed for paediatric use, levofloxacin, has however not been approved beyond 14 days of treatment, when a child with drug-resistant tuberculosis would need to take the medicine for close to two years. For cycloserine, different guidelines give different recommendations so there is no clarity regarding the safety and efficacy of the use of this drug in children.

Even when a drug is registered for use in children and a paediatric formulation does exist - for amikacin, for example - it is not included in the GDF product catalogue, meaning that GLC-approved programmes cannot purchase it through the GDF.

The interactions of DR-TB drugs with AIDS medicines are also largely unknown. There is precious little information on how DR-TB drugs interact with antiretroviral medicines used to treat HIV/AIDS[70] - this has not been a priority for developers of HIV drugs as co-infection with TB is today uncommon in wealthy countries. This is particularly problematic given that TB is the biggest killer of people living with HIV today[2].

For many DR-TB medicines the crucial research is lacking. For kanamycin, amikacin and capreomycin, for example, the potential for renal toxicity when used with tenofovir (the backbone of the WHO-recommended first-line antiretroviral regimen) is unstudied. The medicines of the fluoroquinolone class - moxifloxacin, levofloxacin and ofloxacin - are thought to interact with crucial protease inhibitors like ritonavir and atazanavir (both part of second-line AIDS regimens). Drug interactions are also predicted between ethionamide and prothionamide and ARVs such as nevirapine and efavirenz. There is precious little knowledge about possible interactions for other medicines, such as terizidone, PAS and cycloserine.

The adaptability of some DR-TB medicines for use in resource-poor settings is also a concern. Many DR-TB drugs are poorly adapted to the constraints of health systems in high-burden settings. PAS requires refrigeration, which is an added logistical burden for programmes, particularly in sub-Saharan Africa. The use of injectable products like kanamycin and amikacin also imposes burdens both on the programme, as qualified staff will be required for administration of the product, and on the patient, who must undergo six months of painful injections.

R&D for TB: A long story of neglect

The medicines used in DR-TB treatment cause often intolerable side effects, which can include nausea, severe vomiting, depression, aggressive behaviour, hallucinations, vertigo, hearing loss and diarrhoea. With such a litany of complaints associated with drug-resistant tuberculosis treatment, many look to the research and development (R&D) pipelines for a new regimen to answer these problems.

R&D into TB drugs and diagnostics were neglected for decades because the disease primarily affects developing countries and therefore did not represent a lucrative market for the pharmaceutical industry. This applies as much to drug-susceptible as drug-resistant TB. In the case of second-line TB medicines, however, the problem is amplified, as the drugs used are of limited effectiveness, with success rates of the current treatment at around 80% at best.

After having been at a virtual standstill for about 40 years, the TB drug pipeline has seen encouraging progress in recent years[68], with renewed R&D activities by the Global Alliance for TB Drug Development (the product development partnership established in 2000 to foster development of new TB drugs) and a few pharmaceutical companies. However, compared to other disease R&D pipelines, TB's remains fairly limited, and no new drug has yet reached the market.

The objective of the TB Alliance, the leading product development partnership in TB drug R&D, is to deliver a new regimen able to treat both drug-sensitive and drug-resistant TB, shorter than current first-line treatment and compatible with HIV treatment[69]. Currently there are ten new or repurposed compounds in the clinical development stage and the intention is that some of them will be part of a future single treatment regimen active against both drug-sensitive and all forms of drug-resistant TB[18].

It is questionable whether this objective can be achieved within reasonable timelines. In addition, the most urgent priority is to improve treatment of MDR-TB, given length, toxicity and limited effectiveness of current treatment.

Among the new drugs, Tibotec's TMC207[19] and Otsuka's OPC67683[20] are in most the advanced stages, and have recently completed Phase IIb clinical trials in MDR-TB patients. TMC 207 is expected to get accelerated approval for use in DR-TB treatment as early as 2012. However, further studies will be needed to determine if the addition of the new drug will allow some of the older drugs to be removed from the regimen and how much the treatment regimen can be shortened.

To ensure a range of effective treatment options in the long-term, a large number of new drug candidates with novel mechanisms of action need to be available to allow for the selection of optimum regimens and meet the goal of a single therapy effective against both drug-sensitive and drug-resistant TB. Thus drug discovery efforts need to be scaled up in order to have a healthy pipeline able to deliver an optimal treatment regimen.

In the immediate term, it is crucial to make today's DR-TB treatment as tolerable as possible for patients. This entails conducting studies on how to alleviate the worst side effects caused by existing drugs, by for example looking at ways to space the intake of drugs, optimise doses, develop alternative, more user-friendly formulations (for the injectables) and study their use in children and people living with HIV.

Part of these efforts involve exploring new combinations of existing medicines to reduce the duration of treatment[21]. A shorter regimen has already been used in Bangladesh, the results of which have been recently published. Based on this experience, The Union will conduct a clinical trial of this shortened regimen and will begin enrolling patients in 2011.

Photo © Krisanne Johnson

MDR-TB patient in Swaziland awaits painful daily injection

Conclusions: Breaking the vicious circle

Untreated DR-TB kills and further encourages the disease's spread. But with insufficient numbers of patients on treatment, demand for DR-TB drugs is low, and the market for the development and production of DR-TB drugs remains unattractive. This creates a vicious circle because limited drug supplies in turn contribute to hindering the scale up of DR-TB treatment. As demand stays low, not least for WHO quality-assured drugs, there is little incentive either for new producers to enter the market or for existing producers to invest in meeting WHO quality standards or increasing production capacity. Supply insecurity due to delivery delay or interruption - as for kanamycin in 2010 - means that programmes have been cautious rather than ambitious about the number of people they aim to treat - a direct disincentive to treatment scale-up.

Low demand for DR-TB drugs is also caused by the difficulties surrounding diagnosis - only 11% of 440,000 new MDR-TB cases were detected in 2009. Until now, it has taken up to three months to determine a patient's precise drug-resistance profile, and diagnosis of TB is especially complicated in both people living with HIV/AIDS and children.

However, a new diagnostic tool based on molecular technology could help break open the vicious circle by dramatically shortening the time it takes to determine whether someone has TB to 90 minutes[49]. It can also determine whether a patient is resistant to one of the main first-line drugs to treat TB. Endorsed in December 2010 by the World Health Organization, the test is being rolled out in MSF programmes in 15 countries this year. If the new test is implemented more widely, improved diagnosis could contribute to the level of increased demand needed to make the DR-TB drug market more attractive to drug developers and manufacturers. This, in turn, could lead to additional suppliers entering the market and seeking WHO quality assurance, and prices decreasing.

A number of targeted interventions are also needed to stimulate the MDR-TB drug market. The framework of the Green Light Committee Initiative and the work of the Global Drug Facility may have made an important contribution but have not yet been able to overcome supply problems and decrease prices. The GLC Initiative and the GDF have been undergoing a reform process since early 2010 - what is needed is for GDF to take a clear break from its previous short-term approach and limited focus on risk minimising strategies. The GDF can and should play a stronger market shaping role, guided and supported by users and donors.

The Global Drug Facility:

- Should publish prices of medicines procured on its website in order to improve transparency.
- Should no longer restrict sale of quality-assured medicines to GLC-approved programmes. All treatment programmes should be able to buy quality-assured medicines, as currently envisioned as part of the GLC reform;
- Should further develop and pursue the activities outlined as a part of its 'Roadmap for MDR-TB Scale Up', which lists a number of market interventions to attract new suppliers. This roadmap includes:
  - giving manufacturers long-term contracts to ensure increased production volumes;
  - a strategic revolving fund to provide manufacturers a financial guarantee while countries await fund disbursement;
  - providing manufacturers with reliable demand forecasting per country, both in the short and in the longer term;
  - the expansion of the existing rotating stockpile to decrease the time it takes for countries to receive medicines.
  - a transparent market share allocation mechanism to manufacturers to provide incentives to manufacturers to participate in GDF procurement.

Manufacturers and drug developers:

- Should agree to provide information on prices and pricing conditions in order to improve the transparency on the price of DR-TB medicines
- Should broadly register their products in endemic countries
- Should invest in production and WHO prequalification of existing DR-TB drugs, and develop paediatric formulations adapted to resource limited settings, anticipating an international treatment scale up;
- Drug developers currently investing in the development of new TB drugs should trial their compounds in DR-TB patient populations. Efforts should be undertaken to make new drugs available as quickly as possible via compassionate use and expanded access programmes.
- Drug developers should study the safety and efficacy of existing and new medicines in paediatric formulations and for possible drug interactions with antiretrovirals.

Countries affected by TB:

- Should ensure that first-line treatment is continuously available for TB patients to prevent generating new MDR-TB cases;
- Should invest in the scale up of DR-TB treatment including investment in increased diagnostic and programmatic capacity to enrol progressively more patients on treatment. Innovative models for community-based treatment that allow to reach more patients and better are showing good results and should be supported;
- Should commit to purchase only quality-assured medicines. This will benefit patients and act against further resistance development but will also help to create increased economies of scale for quality-assured products;
- High-level support is needed in many high-burden countries to ensure fast track registration of DR-TB medicines or easier mechanisms for importation;
- Good in-country drug management systems are needed to ensure continued drug supply at programme level and input into reliable international drug forecasting.

Donors:

- Have an important role to play to guide and support financially the market interventions outlined in the GDF's Roadmap, as these are needed to improve international DR-TB drug supply and reduce prices;
- Donors' support will be critical to ensure international treatment scale-up, although many DR-TB high-burden countries have contributed and need to continue contributing significant resources to MDR-TB programmes. It has been estimated that $16.2 billion are needed between 2010-2015 to support treatment in the 27 high-burden countries; and
- Donors should support research to define a better and shorter DR-TB treatment regimen with the inclusion of newer drugs.

Photo © Ivan Sigal

MDR-TB patient receives care through MSF in Uzbekistan

KANAMYCIN (Km)

General Information

- Therapeutic Class: Aminoglycoside antibiotic
- ATC Code: J01GB04[22]
- Included in the WHO Guidelines as Group 2 injectable agent[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] and in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: solution for injection: 1g/4ml, 500mg/2ml, 1g/3ml. As powder for injection: 1g
- First approved by U.S. Food and Drug Administration (FDA): The date of the original New Drug Application (NDA) is not publically available on the US FDA website. The first Abbreviated New Drug Application (ANDA) was approved on 13 February 1973. The only registered product in the US today 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 microorganisms[44]

Price (in US$) and quality information

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

Manufacturer	Meiji	Panpharma	Macleods	APP Pharma	GDF pooled procurement price
Quality status	Approved by SRA	Approved by SRA	Under evaluation	Approved by SRA	GDF Quality Assurance Policy
1g powder for injection	xx	0.84*	No price information given	xx	No price information given
1g/4ml solution for injection	No price information given	xx	xx	xx	2.58 (Meiji)
1g/3ml solution for injection	xx	xx	xx	Not currently in production	xx

* Price received in Euro and converted to US$ on 7 March 2011

There is no clinical difference between kanamycin and amikacin. They have similar side effect profiles and show cross reactivity and therefore almost identical resistance[23]. The choice of a National TB Programme or treatment provider will also therefore depend on other factors including price, availability and adaptability of the formulation.

Number of quality sources

In the past, kanamycin formulations from several different manufacturers were registered in the US. Today, however, only three kanamycin products approved by a stringent regulatory authority were identified in this report. No sources of kanamycin are approved through WHO Prequalification, although one manufacturer (Macleods) has submitted a dossier to WHO Prequalification and has been accepted for evaluation.

Despite this, the supply of kanamycin remains vulnerable to disruption. Today, only one company (APP Pharma) has an active registration in the US - but they have not had any production since February 2009 due to the relocation of the API manufacturer[26]. In the EU, there is only one approved manufacturer (Panpharma) but in 2010 they had a problem with the API resulting in an interruption in supply. As this was the only quality-assured source available to GDF at the time, this resulted in a significant problem for GLC-approved programmes and other treatment providers. The problem has been rectified but capacity issues remain.

In reaction to the potential shortage of quality-assured kanamycin, GDF identified an alternative source in Japan (Meiji). While this helped to ensure continual supply while Panpharma was not in production, Meiji has limited production capacity and the price is considerably more than the Panpharma product. The supply is also reserved for GDF leaving other treatment providers with no alternative quality-assured sources.

This is a good example of the vulnerability of supply with limited sources. Additional manufacturers may exist in China, India, the former Soviet Union, and other countries, but whether they comply with WHO quality standards is unknown.

Active Pharmaceutical Ingredient

Increasing the number of quality-assured sources for the finished product is to a large extent tributary of the difficulties associated with the production of the active pharmaceutical ingredient (API).

Kanamycin API is manufactured by a process of fermentation. This is a specialised process, and there are not many manufacturers globally who have the capacity to produce quality-assured API produced through the fermentation process - the complexity is further increased as the API should be sterile. In today's regulatory environment, the quality assurance of the API is critical in the approval process of the finished product through WHO Prequalification or a stringent regulatory authority.

Evolution in price

In 2001, Green Light Committee-approved programmes were able to access kanamycin for US$ 0.36 per vial[27]. Since then the price has slowly increased and today the most affordable price available through the GDF, for a fully liquid ampoule, is more than seven times the price offered to the GLC in 2001. The reason for this is not clear, but partially this is related to the unavailability of the Panpharma product in 2010, and the identification of Meiji as a quality-assured alternative. The Panpharma price offered to this report is still more than double the 2001 price, but due to capacity issues this source is not assured.

Adaptability

Kanamycin, like the other aminoglycosides and capreomycin cannot be administered orally. This imposes burdens both on the programme, as qualified staff will be required for administration of the product, and on the patient, who must undergo six months of painful injections.

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

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

HIV co-infection

There have been no studies performed, but based on pharmacokinetic profiles, the potential for drug interactions are low. There is however potential for additive toxicities in particular with antiretrovirals which may cause renal toxicity like tenofovir[28]. Further studies are required to confirm this.

AMIKACIN (Am)

General Information

- Therapeutic Class: Aminoglycoside antibiotic
- ATC Code: J01GB06[22]
- Included in the WHO Guidelines as a Group 2 injectable agent[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] and in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: solution for injection: 500mg/2ml; 100mg/2ml. As powder for injection: 100mg, 500mg & 1g
- First approved by U.S. Food and Drug Administration (FDA): The date of the original New Drug Application (NDA) is not publically available on the US FDA website. The first Abbreviated New Drug Application (ANDA) was approved on 22 January 1981[45]
- Approved indication in the US: Amikacin is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including bacterial septicemia (including neoatal 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 postoperative infections (including postvascular surgery)[46]

Price (in US$) and quality information

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

Manufacturer	Medochemie	Cipla	Help SA	GDF pooled procurement price
Quality status	Approved by SRA	Approved by WHO PQ	Approved by SRA	GDF Quality Assurance Policy
500mg/2ml solution for injection	1.06*	No price information given	1.54*	1.20* (Medochemie)

* Price received in Euro and converted to US$ on 7 March 2011

There is no clinical difference between kanamycin and amikacin. They have similar side effect profiles and show cross reactivity and therefore almost identical resistance[23]. The choice of a National TB Programme or treatment provider will therefore depend on other factors including price, availability and adaptability of the formulation.

Number of quality sources

Several companies have amikacin approved by stringent regulatory authorities. In addition, in January 2011, the first generic amikacin from Cipla was prequalified by WHO. A further Indian manufacturer (Micro Labs) is expected to submit a dossier to WHO Prequalification during the course of 2011.

There are multiple sources of quality-assured amikacin, possibly because other approved indications of use exist for the drug. The supply of amikacin is therefore secure.

Evolution in price

In 2001, Green Light Committee-approved programmes were able to access amikacin for US$ 0.11 per vial or ampoule[27]. Since then, the price has slowly increased and today the most affordable price available through the GDF is $1.20 per vial or ampoule. This is an increase of close to 1000% since 2001, the reasons for which are unclear.

Nevertheless this remains considerably more affordable than prices paid in rich countries - the British National Formulary lists a price of $16.49 per vial[29,30].

Adaptability

Amikacin, like the other aminoglycosides and capreomycin cannot be administered orally. This imposes burdens both on the programme, as qualified staff will be required for administration of the product, and on the patient, who must undergo six months of painful injections.

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

Paediatrics

Amikacin is licensed for use in neonates, infants and children[31]. There is a smaller dosage (100mg/2ml) available which allows for more accurate dosing in children.

No prices were offered for this product for this report. In addition, the GDF does not include this formulation in its product catalogue, meaning that GLC-approved programmes cannot order this product for children through the GDF[32].

HIV co-infection

There have been no studies performed, but based on pharmacokinetic profiles, the potential for drug interactions are low. There is however potential for additive toxicities in particular with antiretrovirals which may cause renal toxicity like tenofovir[28]. Further studies are required to confirm this.

CAPREOMYCIN (Cm)

General Information

- Therapeutic Class: polypeptide antibiotic
- ATC Code: J01GB06[22]
- Included in the WHO Guidelines as a Group 2 injectable agent[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] and in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: 1g powder for injection
- First approved by U.S. Food and Drug Administration (FDA): 2 June 1971[33]
- Approved indication in the US: Capreomycin is to be used concomitantly with other appropriate anti-tuberculosis agents, is indicated 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[33]

Price (in US$) and quality information

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

Manufacturer	Akorn	Macleods	GDF pooled procurement price
Quality status	Approved by SRA	Under evaluation	GDF Quality Assurance Policy
1g powder for injection	8.00	No price information given	4.00* (Eli Lilly)

* In future, the price will change as the Akorn product replaces Eli Lilly's.

Number of quality sources

Eli Lilly filed the initial application to the US FDA in 1971. Since 2003, the company has been actively engaged in technology transfer to three generic manufacturers (Aspen, Hisun and SIA International) and today has ceased production of capreomycin in the US. None of these manufacturers has yet received regulatory approval by a SRA or WHO PQ.

Today, there are no sources of capreomycin approved through WHO PQ. In the US, Eli Lilly's license was sold to Akorn, which today is the only quality-assured source available to GDF. An additional manufacturer (Macleods) has submitted a dossier to WHO Prequalification and has been accepted for evaluation, and Aspen is expected to submit during the course of 2011.

The supply of quality-assured capreomycin therefore remains vulnerable to disruption. Additional manufacturers may exist in China, India, the former Soviet Union, and other countries, but whether they comply with WHO quality standards is unknown.

Active Pharmaceutical Ingredient

Increasing the number of quality-assured sources for the finished product is to a large extent tributary of the difficulties associated with the production of the active pharmaceutical ingredient (API).

Capreomycin API is manufactured by a process of fermentation. This is a specialised process, and there are not many manufacturers globally who have the capacity to produce quality-assured API produced through the fermentation process - the complexity is further increased as the API should be sterile. In today's regulatory environment, the quality assurance of the API is critical in the approval process of the finished product through WHO Prequalification or a stringent regulatory authority.

Eli Lilly transferred the technology for capreomycin API to only one manufacturer - the Chinese generic producer Hisun in 2003. Although this has been a success, with the Hisun API being approved by the US FDA in June 2006, all manufacturers of quality-assured capreomycin are reliant on this one source.

Although other API manufacturers exist, none of them has yet been approved by a stringent regulatory authority or by the WHO Prequalification Programme.

Evolution in price

In 2001, Green Light Committee-approved programmes were able to access capreomycin for US$ 1.02 per vial[27]. Since this time, the price has increased, with prices reported in the Global Fund Price and Quality Reporting (PQR) Tool between 2007 and today ranging between $3.21 and $3.64 per vial.[64]

For a number of years, Eli Lilly subsidised the price of the capreomycin for programmes approved by the Green Light Committee. Since transferring the technology to other manufacturers, however, the price of capreomycin has increased by almost 300%. Now that Eli Lilly has ceased production for this market, the price will not be subsidised anymore and we will see a further increase in prices.

The price currently quoted by GDF for this report corresponds to the Eli Lilly subsidised price as stock is still available. We can therefore expect to see a further price increase in the future as GDF turns to Akorn for supplies. If the price Akorn charges for GDF remains the same as the one the manufacturer provided for this document ($8), the impact on the overall cost of a drug-resistant tuberculosis treatment containing capreomycin will be an increase of around $720.

Nevertheless the Akorn price remains considerably more affordable than prices paid in rich countries - the British National Formulary lists a price of $40.95 per vial[29,30].

Adaptability

Capreomycin, like DR-TB medicines from the aminoglycosides class, cannot be administered orally. This imposes burdens both on the programme, as qualified staff will be required for administration of the product, and on the patient, who must undergo six months of painful injections.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

HIV co-infection

There have been no studies performed, but based on pharmacokinetic profiles, the potential for drug interactions are low. There is however potential for additive toxicities in particular with antiretrovirals which may cause renal toxicity like tenofovir[28]. Further studies are required to confirm this.

MOXIFLOXACIN (Mfx)

General Information

- Therapeutic Class: Fluoroquinolone
- ATC Code: J01MA14[22]
- Included in the WHO Guidelines as a Group 3 Fluoroquinolones[23]
- Not included in the 16th edition of the WHO Model List of Essential Medicines[24] nor in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: 400mg tablet
- First approved by U.S. Food and Drug Administration (FDA): 12 October 1999[71]
- 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[35]

Price (in US$) and quality information

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

Manufacturer	Macleods	Cipla	Bayer	GDF pooled procurement price
Quality status	Under evaluation	Approved by WHO PQ	Approved by SRA	GDF Quality Assurance Policy
400mg tablet	No price information given	No price information given	No price information given	1.70 (Cipla)

Number of quality sources

For many years, Bayer was the only quality-assured source of moxifloxacin available. In November 2010, the first moxifloxacin was prequalified by WHO (Cipla) and a second manufacturer (Macleods) has submitted a dossier that has been accepted for evaluation. The supply of moxifloxacin will therefore be relatively secure in the near future (although price remains a barrier).

In addition, we can expect to see further sources of quality-assured moxifloxacin, because other approved indications of use exist for the drug. Indeed, there are two generic manufacturers (Dr Reddy's and Teva) that have US FDA tentative approval, waiting to enter the US market when the patent expires.

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

Evolution in price

With the entry of a quality-assured generic into the market the price has reduced considerably. Prior to this the only option available was Bayer and prices for this product reported in the Global Fund Price and Quality Reporting (PQR) Tool between 2009 and today range between US$ 3.97 and $5.03 per tablet.[64]

This shows that some developing countries are therefore paying prices higher than those paid in rich countries - the British National Formulary lists a price of $4.03 per tablet[29,30]. With more generic manufacturers expected to enter the market, we could expect to see this price continue to fall.

Approved Indication

While moxifloxacin has been shown to be effective against *Mycobacterium Tuberculosis* (Mtb)[36] and has been included in many guidelines for use in DR-TB, it does not have an indication approved by any stringent regulatory authority. When moxifloxacin is used as a part of a DR-TB treatment regimen, it is therefore essentially being used “off label” for this indication. This may increase complexities for manufacturers trying to register their products for the indication of TB in some countries.

In August 2005, Bayer and TB Alliance signed an agreement to conduct a global clinical development programme, aiming to register moxifloxacin for a first-line TB indication. Three Phase II trials have been completed, and a Phase III trial is ongoing.

Other actors, including The Union, are currently involved in clinical trials looking at the use of moxifloxacin in a regimen to shorten the treatment of MDR-TB[21].

Patents

Although patents covering the moxifloxacin molecule have now expired in most countries, subsequent patents claiming a crystal monohydrate form of moxifloxacin appear to stand in the way of generic production. Such patents, due to run until 2016, have been granted in several countries including China, Russia, South Africa and Ukraine.

In India, where this patent was withdrawn by Bayer, additional patents on other pharmaceutical forms have been granted but do not appear to be blocking generic manufacture.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children. As there is no paediatric formulation available today, paediatric doses are obtained by manipulating adult formulations to achieve target doses. Today the only quality-assured adult source available through the GDF does not have a break line to allow for accurate fractioning of the dose.

One alternative is to use an extemporaneously prepared moxifloxacin oral suspension, the subject of a stability study published in 2009[38]. This suspension allows for a more accurate way to measure and administer a dose to a child. However, preparing this formulation requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent. This solution is far from ideal and there is therefore a need for a commercially available paediatric formulation.

HIV co-infection

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

Protease inhibitors and efavirenz may prolong QT interval so concomitant use with moxifloxacin should be cautious, with electrocardiogram monitoring. Oral absorption of fluoroquinolones are reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets[28].

LEVOFLOXACIN (Lfx)

General Information

- Therapeutic Class: Fluoroquinolone
- ATC Code: J01MA12[22]
- Included in the WHO Guidelines as a Group 3 Fluoroquinolones[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] and in 2nd edition of the WHO Model List of Essential Medicines for Children[25]. 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 U.S. Food and Drug Administration (FDA): 20 December 1996. The paediatric formulation (25mg/ml oral solution) was approved on 21 October 2004[40]
- 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)[40]

Price (in US$) and quality information

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

Manufacturer	Cipla	Macleods	GDF pooled procurement price
Quality status	Under evaluation	Under evaluation	GDF Quality Assurance Policy
250mg tablet	No price information given	No price information given	0.05 (Macleods)
500mg tablet	No price information given	No price information given	0.08 (Macleods)

Number of quality sources

Two manufacturers have dossiers submitted and accepted for evaluation by WHO Prequalification. These Cipla (250mg) and Macleods (250mg and 500mg) sources have already been assessed by the Expert Review Panel for the GDF and the Global Fund and are currently listed as purchasable in 2011 with Global Fund money.

An additional manufacturer (Micro Labs) is expected to submit to WHO Prequalification during the course of 2011. The supply of levofloxacin is therefore relatively secure.

In addition, there are multiple sources of quality-assured levofloxacin, because other approved indications of use exist for the drug. Indeed, a further 13 manufacturers have obtained US FDA tentative approval for levofloxacin, waiting to enter the US market when the patent expires in the US in June 2011. However, none of these producers have applied for WHO Prequalification, nor have made their products available to GDF.

Evolution in price

The prices reported in the Global Fund Price and Quality Reporting (PQR) tool between 2007 and today has remained at US$ 0.05 per 250mg tablet, and has varied between $0.05 and $0.10 per 500mg tablet[34].

This remains considerably more affordable than prices paid in rich countries - the British National Formulary lists a price of $2.36 per 250mg tablet and $4.21 per 500mg tablet[29,30]. The price of levofloxacin does not appear to be an issue.

Approved Indication

While levofloxacin has been shown to be effective against *Mycobacterium Tuberculosis* (Mtb)[36] and has been included in many guidelines for use in DR-TB, it does not have an indication approved by any stringent regulatory authority. When levofloxacin is used as a part of a DR-TB treatment regimen, it is therefore essentially being used "off license" for this indication. This may create problems for manufacturers trying to register their products for the indication of TB in some countries.

Patents

Patents claiming levofloxacin were originally filed in 1981[65] and 1986[66] by Daiichi Seiyaku, now a subsidiary of Daiichi Sankyo, and licensed to Janssen. Although 20-year patents expired in 2001 and 2006 respectively, patent protection has been extended until June 2011 in several European countries and the US.

As the patent will expire soon, manufacturers are already registering their product in the US and the EU. Those manufacturers should be contacted by GDF to see if they could be interested, once the patent has expired, in also supplying GLC-approved programmes.

Paediatrics

Levofloxacin has been approved in the US for children aged over six months, but only for use in children for acute infections. The safety in paediatric patients treated for more than 14 days has not been studied. Because children with DR-TB may be treated with this drug up for up to two years, there is therefore a need for more safety data on the use of levofloxacin for extended periods of time in children.

Children metabolise levofloxacin faster than adults and smaller children need to receive doses twice a day rather than daily as recommended for adults. This can be difficult to implement programmatically if strict directly observed therapy is followed. The US-approved product information suggests twice a day dosing for children between six months and 17 years. Other publications suggest twice a day dosing for under five years, while the WHO guidelines suggest a once a day dosing. This can be confusing to National TB Programmes and dangerous for children. There is a need for a further clarification and a consensus on the dosing of small children.

While there is paediatric formulation (25mg/ml oral solution) available in the US, this is not widely available elsewhere. There has been a study published looking at the stability of an extemporaneously prepared levofloxacin oral suspension[39]. This suspension allows for a more accurate way to measure and administer a dose to a child. However, preparing this formulation requires a certain level of training, supervision and resources, which may not be available in many settings where DR-TB is prevalent.

The reality today is adult formulations are manipulated in order to achieve target doses. Today the only quality-assured source available through GDF does not have a break line to allow for accurate fractioning of the dose. Both of these solutions are far from ideal and there is therefore a need for the paediatric formulation to be made more widely available.

HIV co-infection

No interaction studies have been performed, but based on the knowledge of the metabolism of levofloxacin, no interactions are predicted. Further research is needed to assess this. Protease inhibitors and efavirenz may prolong QT interval so concomitant use with levofloxacin should be cautious, with electrocardiogram monitoring. Oral absorption of fluoroquinolones is reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets[28].

OFLOXACIN (Ofx)

General Information

- Therapeutic Class: Fluoroquinolone
- ATC Code: JJ01MA01[22]
- Included in the WHO Guidelines as a Group 3 Fluoroquinolones[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] nor in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: 200mg, 300mg, 400mg tablet
- First approved by U.S. Food and Drug Administration (FDA): 28 December 1990[71]
- Approved indication in the US: Ofloxacin is approved for the indications of acute bacterial exacerbations of chronic bronchitis, acute uncomplicated uretheral and cervical gonorrhea, non-gonococcal urethritis and cervicitis, acute pelvic inflammatory disease and uncomplicated skin and skin structure infections[41]

Price (in US$) and quality information

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

Manufacturer	Cipla	Macleods	GDF pooled procurement price
Quality status	Under evaluation	Under evaluation	GDF Quality Assurance Policy
200mg tablet	No price information given	No price information given	0.06 (Macleods)
400mg tablet	No price information given	No price information given	0.06 (Macleods)

Number of quality sources

Today there is no ofloxacin approved by WHO PQ, but three manufacturers (including Cipla and Macleods) have dossiers submitted and accepted for evaluation, and an additional manufacturer (Micro Labs) is expected to submit during the course of 2011. The supply of ofloxacin will therefore be relatively secure in the near future.

In addition, there are multiple sources of quality-assured ofloxacin, because other approved indications of use exist for the drug. As the patent for ofloxacin has now expired, there are three generic manufacturers (Ranbaxy, Teva, and Dr. Reddy's) that have products available on the US market and several others on the EU market, but none of them have made their products available to GDF.

Evolution in price

In 2001, Green Light Committee-approved programmes were able to access ofloxacin for US$ 0.33 per tablet[27]. Since then, the price has decreased dramatically with prices reported in the Global Fund Price and Quality Reporting (PQR) Tool between 2007 and today ranging between $0.03 and $0.06 per 200mg tablet and between $0.05 and $0.07 per 400mg tablet[64]. These prices remain considerably more affordable than prices paid in rich countries - the British National Formulary lists a price of $1.09 per 200mg tablet and $0.89 per 400mg tablet[29,30].

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

Approved Indication

While ofloxacin has been shown to be effective against *Mycobacterium Tuberculosis* (Mtb)[36] and has been included in many guidelines for use in DR-TB, it does not have this indication approved by any stringent regulatory authority. When ofloxacin is used as a part of a DR-TB treatment regimen, it is therefore essentially being used "off license" for this indication. This may create problems for manufacturers trying to register their products for the indication of TB in some countries.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

As there is no paediatric formulation available today, children's doses are obtained by manipulating adult formulations to achieve target doses. Today the only quality-assured source available through GDF does not have a break line to allow for accurate fractioning of the dose.

HIV co-infection

No interaction studies have been performed, and based on the metabolism of ofloxacin, interactions are not predicted. However one source suggests there may be a potential interaction with atazanavir and lopinavir. There is an urgent need for further research to clarify these inconsistencies regarding drug interactions to guide clinicians on drug dosing[51].

Protease inhibitors and efavirenz may prolong QT interval so concomitant use with ofloxacin should be cautious, with electrocardiogram monitoring.

Oral absorption of fluoroquinolones are reduced by buffered drugs, so doses should be separated from didanosine-buffered tablets[28].

ETHIONAMIDE (Eto)

General Information

- Therapeutic Class: carbothionamides group, derivative of isonicotinic acid[23]
- ATC Code: J04AD03[22]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] and in 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: 250mg tablet
- First approved by U.S. Food and Drug Administration (FDA): 30 April 1965[71]
- 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 when there is intolerance on the part of the patient to other drugs[42]

Price (in US$) and quality information

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

Manufacturer	Lupin	Cipla	Macleods	Pfizer	GDF pooled procurement price
Quality status	Under evaluation	Under evaluation	Approved by WHO PQ	Approved by SRA	GDF Quality Assurance Policy
250mg tablet	0.09	No price information given	No price information given	3.50	0.09 (Macleods)

Prothionamide is the propyl analog of ethionamide. There is complete cross resistance between ethionamide and prothionamide and the two are used interchangeably[43].

Number of quality sources

Today only two ethionamide products are quality-assured; one is prequalified by WHO (Macleods) and Pfizer has the marketing license for ethionamide in the US and Canada. Such a limited number of quality-approved sources means this product is relatively vulnerable to supply disruption.

The situation is likely to improve as a further two manufacturers (Lupin, Cipla) have submitted dossiers to WHO Prequalification and have been accepted for evaluation. The Cipla product has already been assessed by the Expert Review Panel for the GDF and the Global Fund and is currently listed as purchasable in 2011 with Global Fund money. An additional manufacturer (Micro Labs) is expected to submit during the course of 2011.

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

Evolution in price

The current price available directly through manufacturers or through the GDF shows little evolution over the past ten years. In 2001, Green Light Committee-approved programmes were able to access ethionamide for US$0.10 per tablet - the price today is identical[27]. The price of ethionamide does not appear to be an issue.

Pfizer has the marketing license for ethionamide in the US and Canada and does not currently have a pricing structure for other markets.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

As there are no paediatric formulations commercially available today, dosages for children are obtained by manipulation of adult formulations. The one quality-assured source available today is a film-coated tablet that is not breakable, which means that fractioning the tablet is not accurate.

HIV co-infection

There have been no studies performed, but based on pharmacokinetic profiles, drug interactions are predicted. There are potentially interactions with some classes of antiretrovirals and there is an urgent need for further studies to confirm this. There is also potential for additive toxicities in particular with antiretrovirals which may cause hepatotoxicity including efavirenz and nevirapine[28].

PROTHIONAMIDE (Pto)

General Information

- Therapeutic Class: carbothionamides group, derivative of isonicotinic acid[23]
- ATC Code: J04AD01[22]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent[23]
- Not included in the 16th edition of the WHO Model List of Essential Medicines[24] nor in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- 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[50]
- 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[52]

Price (in US$) and quality information

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

Manufacturer	Lupin	Fatol	GDF pooled procurement price
Quality status	Under evaluation	Approved by SRA	GDF Quality Assurance Policy
250mg tablet	0.08	0.14*	0.14* (Fatol)

* Price received in Euro and converted to US$ on 7 March 2011

Prothionamide is the propyl analog of ethionamide. There is complete cross resistance between ethionamide and prothionamide and the two are used interchangeably[43].

Number of quality sources

Today there is only one prothionamide product approved by a stringent regulatory authority (Fatol product in Germany) and none is prequalified by WHO. Such a limited number of quality-approved sources means this product is relatively vulnerable to supply disruption.

The situation is likely to improve as a further manufacturer (Lupin) has submitted a dossier to WHO Prequalification and has been accepted for evaluation, and an additional producer (Micro Labs) is expected to submit during the course of 2011.

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

Evolution in price

The current price available directly through manufacturers or through the GDF shows little evolution over the past ten years. In 2001, Green Light Committee-approved programmes were able to access prothionamide for US$0.10 per tablet - the price today is almost identical[27]. The price of prothionamide does not appear to be an issue.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

As there are no paediatric formulations commercially available today, dosages for children are obtained by manipulation of adult formulations. The only quality-assured source available today does have a break line, which facilitates breaking the tablet in half. However prothionamide has a very unpleasant taste and breaking the tablet is not ideal. There is a need for a paediatric formulation to be made available.

HIV co-infection

There have been no studies performed, but based on pharmacokinetic profiles, drug interactions are predicted. There are potentially interactions with some classes of antiretrovirals and there is an urgent need for further studies to confirm this. There is also potential for additive toxicities in particular with antiretrovirals which may cause hepatotoxicity including efavirenz and nevirapine[28].

CYCLOSERINE (Cs)

General Information

- Therapeutic Class: analog of D-alanine[23]
- ATC Code: J04AB01[22]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines[24] and in 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: 250mg capsule
- First approved by U.S. Food and Drug Administration (FDA): 29 June 1964[71]
- 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[53]

Price (in US$) and quality information

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

Manufacturer	Lupin	Aspen	Macleods	Purdue GMP	GDF pooled procurement price
Quality status	Under evaluation	Approved by WHO PQ	Approved by WHO PQ	Approved by SRA	GDF Quality Assurance Policy
250mg capsule	0.60	0.78	No price information given	No price information given	0.59 and 0.78 (Macleods and Aspen)

Number of quality sources

Eli Lilly filed the initial application to the US FDA in 1964. Since 2003, the company has been actively engaged in technology transfer to three generic manufacturers (Aspen, Purdue GMP and SIA International) and in 2008 ceased production of cycloserine. Two of these manufacturers (Aspen & Purdue GMP) now produce quality-assured cycloserine.

In additional, another manufacturer (Macleods) has cycloserine approved by WHO Prequalification and three other manufacturers (including Lupin and Cipla) have submitted dossiers to WHO Prequalification and have been accepted for evaluation.

The supply of quality-assured cycloserine is therefore relatively secure.

Active Pharmaceutical Ingredient

Until 2006, the only quality-assured source for the active pharmaceutical ingredient was Eli Lilly.

Eli Lilly started the technology transfer for the API to Shasun, India, in 2003 a process that was concluded in 2006. This was a success with the Shasun API being approved by the US FDA in June 2008.

Evolution in price

In 2001, Green Light Committee-approved programmes were able to access cycloserine for US$ 0.14 per capsule[27]. Since this time the price has slowly increased, with prices reported in the Global Fund Price and Quality Reporting (PQR) Tool between 2007 and today ranging between $0.48 and $0.68 per capsule[34].

For a number of years, Eli Lilly subsidised the price of the cycloserine for programmes approved by the Green Light Committee. Since transferring the technology to other manufacturers, however, the price of cycloserine has increased by more than 300% to $0.59 per capsule.

This remains considerably more affordable than prices paid in rich countries - the British National Formulary lists a price of $5.43 per capsule[29,30].

Paediatrics

The British National Formulary provides doses for children aged 2 to 18 while the US FDA states that the safety and effectiveness in children has not been established. This is a clear example of different guidelines providing different recommendations. There is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

As there are no paediatric formulations commercially available today, dosages for children are obtained by manipulation of adult formulations. All of the quality-assured sources available today are capsules, which means that it is not possible to accurately fraction the capsule.

HIV co-infection

The metabolism of cycloserine is not completely understood, and hence interactions are unpredictable[28]. There is a need for more research into the interactions between antiretrovirals and cycloserine.

TERIZIDONE (Trd)

General Information

- Therapeutic Class: analog of D-alanine[23]
- ATC Code: J04AK03[22]
- Included in the WHO Guidelines as a Group 4 oral bacteriostatic second-line agent [23]
- Not included in the 16th edition of the WHO Model List of Essential Medicines[24] nor in 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- 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[50]
- Approved indication in Germany: Treatment of tuberculosis in adults and juveniles aged 14 or older[54]

Price (in US$) and quality information

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

Manufacturer	Fatol	GDF pooled procurement price
Quality status	Approved by SRA	GDF Quality Assurance Policy
250mg capsule	1.68*	1.65* (Fatol)

* Price received in Euro and converted to US$ on 7 March 2011

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[54]. It is being used in some countries instead of cycloserine, and assumed to be as efficacious; however, there are no direct studies comparing the two drugs, and terizidone is therefore not yet recommended by WHO[23].

Number of quality sources

Today there is only one quality-assured source of terizidone available. There are no manufacturers with dossiers submitted to WHO PQ, and no manufacturers likely to submit dossiers in 2011. The supply of quality-assured terizidone therefore remains extremely vulnerable to disruption.

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

Evolution in price

No price for terizidone was reported in the Global Fund Price and Quality Reporting (PQR) Tool.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

As there are no paediatric formulations commercially available today, dosages for children are obtained by manipulation of adult formulations. The only quality-assured source available today is a capsule, which cannot be accurately fractioned.

HIV co-infection

As terizidone is a combination of a couple of molecules of cycloserine and the metabolism of cycloserine is not completely understood, interactions are unpredictable[28]. There is a need for more research into the interactions between antiretrovirals and terizidone.

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

General Information

- Therapeutic Class: salicylic acid -anti folate[23]
- ATC Code: for PAS: J04AA01 For PAS-Sodium: J04AA02[22]
- Included in the WHO Guidelines PAS: as a Group 4 oral bacteriostatic second-line agent. PAS-sodium: not included[23]
- PAS included in the 16th edition of the WHO Model List of Essential Medicines[24] and in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]. PAS-Sodium is not included in either document.
- Presentations available: PAS: 4g sachet. PAS-Sodium: 60% weight for weight granules 9.2g sachet and 100g jar; powder for solution 5.52g sachet (equivalent to PAS 4g sachet)
- First approved by U.S. Food and Drug Administration (FDA): PAS-Sodium was first registered in a tablet formulation in the US on 8 March 1950. There are no manufacturers of PAS-Sodium on the market in the US today. The only product on the market today in the US is PAS and this was registered on 30 June 1994[55]
- 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[55]

Price (in US$) and quality information

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

Manufacturer	Jacobus	Macleods	Olainfarm	GDF pooled procurement price
Quality status	Approved by SRA	Approved by WHO PQ	Approved by SRA	GDF Quality Assurance Policy
PAS 4g sachet	1.57	xx	xx	1.57 (Jacobus)
PAS-Sodium - 60% w/w granules - 9.2g sachet	xx	No price information given	xx	No price information given
PAS-Sodium - 60% w/w granules - 100g jar	xx	No price information given	xx	24.00 (2.21)* (Macleods)
PAS-Sodium - powder for solution- 5.52g sachet	xx	xx	No price information given	1.50 (Olainfarm)

*Price of 9.2g (equivalent to 4g of PAS) of this formulation

Para-aminosalicylate sodium (PAS - Sodium) is the sodium salt of para-aminosalicylic acid (PAS). 1.38g of PAS-Sodium is approximately equivalent to 1g of PAS[56]. None of the quality-assured sources of either PAS or PAS-Sodium come in the same formulation as each other, which means depending on the product, different doses of granules and powders are required to deliver the same quantity of PAS. This can be can be particularly confusing if multiple formulations exist in one treatment programme.

Number of quality sources

Today there is only one quality-assured source of PAS (Jacobus), and two quality-assured sources of PAS-sodium (Macleods and Olainfarm), with no products in the pipeline. This means the supply of quality-assured product is vulnerable.

The PAS-Sodium formulation from Macleods was approved by WHO PQ in 2009, but the unexpectedly large demand for this product led to capacity problems, resulting in long lead times for orders. This should be rectified in 2011.

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

Evolution in price

In 2001, Green Light Committee-approved programmes were able to access PAS for US$1.51 per 4g sachet[27]. Since this time the price has slowly increased, with prices for this product reported in the Global Fund Price and Quality Reporting (PQR) Tool between 2007 and today ranging from $1.88 and $2.00 per 4g sachet.

Heat-stable PAS-Sodium is available today range in price between $1.5 and $2.21 for an equivalent dose of PAS.

While the price of PAS and PAS-Sodium has remained relatively stable in recent years, the medicine accounts for between 25 and 50% of the total cost of a patient's treatment overall cost, depending on which medicines and which products are used. A reduction in the price of PAS and PAS-Sodium would therefore have a large impact on the overall cost of treatment.

Adaptability

The PAS marketed by Jacobus, must be stored at temperatures 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.

The product information states “the packets may be stored at room temperature for short periods of time”. This should be clarified to give treatment providers guidance on the exact length of time the product may be stored above 15°C before dispensing to patients, without risk of degradation. The availability of a PAS product that can be kept at room temperature for a determined period of time will have positive implications, especially where programmes are moving to a decentralised approach and may not have access to cold chain.

The PAS-Sodium products do not require any special storage conditions.

Paediatrics

The safety and effectiveness in children has not been established. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

As there are no paediatric formulations commercially available today, dosages for children are obtained by manipulation of adult formulations. As all the available formulations are either granules or powders, measuring the exact dose for a child is difficult and requires calibrated scales to be available at the point of dispensing. The PAS-Sodium product from Macleods that is supplied in the 100g jar is however supplied with a graduated measuring cup to allow for some estimations of dose, but this is still not accurate enough.

An additional complexity is that dosages are not given for PAS-Sodium, and that doses have to be calculated based on the content of PAS in PAS-Sodium. This has the potential to increase the risk of prescribing and dispensing errors.

There is therefore a need for a commercially available paediatric formulation.

HIV co-infection

There have been no studies performed, but based on the pharmacokinetic profile of the PAS, drug interactions are unlikely. Studies should be performed to confirm this[28].

CLOFAZIMINE (Cfz)

General Information

- Therapeutic Class: Phenazine Derivative[23]
- ATC Code: J04BA01[22]
- Included in the WHO Guidelines as a Group 5 medicine; agents with unclear efficacy[23]
- Included in the 16th edition of the WHO Model List of Essential Medicines (as an anti-leprosy medicine)[24] and in the 2nd edition of the WHO Model List of Essential Medicines for Children (as an anti-leprosy medicine)[25]
- Presentations available: 50mg and 100mg soft-gel capsules
- First approved by U.S. Food and Drug Administration (FDA): 15 December 1986[57]
- Approved indication in US: Clofazimine is indicated in the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum[57]

Price (in US$) and quality information

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

Clofazimine is a Group 5 medicine which today represents a very small market, as they are essentially used in patients with XDR-TB. While there is a quality-assured source available, Novartis was not contacted regarding a price for this product. This medicine does not exist in the GDF product catalogue.

Clofazimine was first synthesised in 1954 as an anti-TB compound. The drug was thought to be ineffective against TB but in 1959 effectiveness against leprosy was demonstrated. After clinical trials the product was launched in 1969 and marketed by Novartis for use in leprosy.

Even though clofazimine has no official indications for the treatment of DR-TB, clinical data on use in TB has been published and the drug is recommended by WHO.

Number of quality sources

Today there is only one source approved by a stringent regulatory authority. This product is produced by Sandoz for Novartis. Additional manufacturers may exist in China, India, the former Soviet Union and other countries, but whether they comply with WHO quality standards is unknown.

Clofazimine was not included in the 10th Invitation to Manufacturers to submit an Expression of Interest (EoI) for product evaluation by WHO Prequalification (August 2010 - revised February 2011). Because of this, there are no manufacturers with dossiers currently under evaluation. The drug was however included in the joint GDF/Global Fund Invitation to manufacturers to submit an Expression of Interest for product evaluation issued by the Expert Review Panel in January 2011.

With no market for this product in wealthy countries, there is no reason for a manufacturer to seek authorisation through a stringent regulatory authority. It is therefore imperative that WHO Prequalification includes clofazimine in the next EoI, to send a clear message to manufacturers that the product is needed.

Even if demand is low, there is a need to have an alternative source to the Novartis product which is not easily available and/or too expensive.

Evolution in price

In late 1999, Novartis signed a Memorandum of Understanding (MoU) with the WHO leprosy programme for a donation of clofazimine and rifampicin[47]. In November 2005, this donation was extended until the end of 2010.

For patients who require this drug, it can be purchased through certain private pharmacies, but the cost is quite high, at US$ 0.86 for the 50mg capsule and $1.43 for the 100mg capsule in Switzerland, for example[58].

Paediatrics

The safety and effectiveness in children has not been established, but several case reports of children treated with clofazimine have been published in the literature. While there are dosages published in several guidelines, there is an urgent need for further research (pharmacokinetics, pharmacodynamics, safety data), into the use of this drug in the younger populations, in particular children aged under five, so that dosages can be clarified and child adapted formulations developed to be able to deliver these dosages to children.

Today there is a 50mg soft-gel capsule available, but this formulation makes it impossible to fraction the dose, and clinicians are put in a difficult position to either over-dose the child and increase the risk of side effects or under-dose and increase the risk of amplification of the child's resistance profile. This is far from ideal.

HIV co-infection

There have been no studies performed, but clofazimine is a weak inhibitor of CYP3A4, and so protease inhibitor and etravirine concentrations may be increased.

Further studies are required to confirm this[28].

LINEZOLID (Lzd)

General Information

- Therapeutic Class: Oxazolidinone antibiotic
- ATC Code: J01XX08[22]
- Included in the WHO Guidelines as a Group 5 medicine; agents with unclear efficacy[23]
- Not included in the 16th edition of the WHO Model List of Essential Medicines[24] nor in the 2nd edition of the WHO Model List of Essential Medicines for Children[25]
- Presentations available: 600mg tablet, 100mg/5ml powder for suspension
- First approved by U.S. Food and Drug Administration (FDA): 18 April 2000[59]
- Approved indication in US: Linezolid is indicated for treatment of susceptible strains of designated microorganisms for the following conditions, nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections. It is not indicated for the treatment of Gram-negative infections and community acquired pneumonia[60]

Price (in US$) and quality information

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

Linezolid is a Group 5 medicine which today represents a very small market, as they are essentially used in patients with XDR-TB. While there is a quality-assured source available, Pfizer was not contacted regarding a price for this product. This medicine does not exist in the GDF product catalogue.

Even though linezolid has been classified by WHO as an agent with unclear efficacy, it has been shown to have in-vitro activity against *Mycobacterium Tuberculosis*. Data has been presented at international conferences and small case series reports have been published on its use in treatment of DR-TB[67]. Linezolid is associated with a relatively high number of adverse effects, including myelosuppression, anaemia and peripheral and optical neuropathies. Linezolid does however play an important role in patients with XDR-TB. Pfizer and Astra Zeneca are currently investigating other medicines in the oxazolidinone group in the hope of developing a more efficacious and safer molecule than linezolid.

Number of quality sources

Today only one manufacturer, Pfizer, is approved by a stringent regulatory authority. A further four manufacturers (Teva, Mylan, Glenmark and Gate Pharma) have tentative approval from the US FDA, waiting to enter the US market when the patent expires.

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

Linezolid was not included in the 10th Invitation to Manufacturers to submit an Expression of Interest (EoI) for product evaluation by WHO Prequalification (August 2010 - revised February 2011). Because of this, there are no manufacturers with dossiers currently under evaluation. The drug was however included in the joint GDF/Global Fund Invitation to manufacturers to submit an Expression of Interest for product evaluation issued by the Expert Review Panel in January 2011.

As linezolid has a market in wealthy countries, manufacturers with SRA approval should be approached to make their products available for the DR-TB market. It is imperative that WHO Prequalification includes linezolid in the next EoI to send a clear message to manufacturers that this product is also needed for the TB market.

Evolution in price

There was no price supplied for linezolid from GDF and no entries reported in the Global Fund Price and Quality Reporting (PQR) tool.

An indicative price is given in the British National Formulary - US$ 72.37 for the 600mg tablet and $361.82 for a 150ml bottle of the paediatric suspension.

The arrival of alternative source will be critical to ensure price reductions.

Patents

The basic patent claiming linezolid was first filed in 1993 by Upjohn Company in the US and is due to expire in May 2015[61]. Similar patents were also granted in China, the Philippines and South Africa.

Upjohn Company also filed patents claiming crystal forms[62] and to a tablet formulation[63] of linezolid in 2001 in many developing countries including Argentina, Brazil, China, Colombia, India, EAPO countries, Mexico, Ukraine and South Africa.

Paediatrics

Pharmacokinetic studies have been completed in children from birth, and dosages are approved by the US FDA. Safety data is based on trials, where patients took linezolid for 28 days. As children with DR-TB may be treated with this drug for up to two years, there is a need for more safety data on the use of linezolid for extended periods of time.

Today there is a paediatric formulation available. It is supplied as a powder for suspension and so requires reconstitution at the point of dispensing. This requires trained staff to accurately measure the required water needed to suspend the powder and access to clean, safe water. The reconstituted product can be stored at room temperature.

HIV co-infection

There have been no studies performed, but interactions are unlikely. There may be increase risk of myelosuppression and mitochondrial toxicities with long-term use in combination with certain antiretrovirals (zidovudine, stavudine, didanosine).[28] Further studies are required to confirm this.

Methodology

This report looks at the sources and prices of 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)[1]. Questionnaires were sent only to companies that had at least one anti-tuberculosis product listed on the WHO List of Prequalified Medicinal Products or quality-approved by a stringent regulatory authority according to MSF or The Union's knowledge. The data were collected up to March 2011.

Price information: Prices are listed where manufacturers agreed to share information. A number of manufacturers, including Cipla, Macleods, Bayer, Meiji, and Olainfarm did not have prices available or did not agree to publish prices, and no responses were received from Eli Lilly, Mylan, Chao Centre and APP Pharma. Prices paid for by the Global Drug Facility pooled procurement mechanism are also listed, although these prices are reserved for projects that have received approval from the Green Light Committee.

Prices are given in US$, rounded up to the nearest second decimal point, and correspond to the lowest unit price (i.e. the price of one tablet, capsule or vial). When prices that varied according to packaging (e.g. blisters or bottle) were received from a manufacturer for the same formulation, the lowest price was selected. Prices received in currencies other than US$ were converted on 7 March 2011 using the currency converter site www.oanda.com. Prices listed are 'ex-works'.

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. The document should not be viewed as a manufacturer's price list, and procurement agents are advised to contact manufacturers directly to confirm prices.

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 the WHO Prequalification or by a stringent regulatory authority are listed in the price tables as 'under evaluation'. Submissions to WHO Prequalification are confidential and all companies mentioned that have the dossier accepted for review have given permission to do so. Products that have not yet been submitted to WHO Prequalification or to a stringent regulatory authority have not been included in the table.

Products procured by the Global Drug Facility 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 approved by the Expert Review Panel (ERP) also used by the Global Fund. The GDF quality assurance policy can be found at: http://www.stoptb.org/gdf/drugsupply/quality_sourcing_process.asp

As the information on the WHO List of Prequalified Medicinal Products is updated regularly, the list should be consulted for up-to-date information regarding quality: http://apps.who.int/prequal/

1 WHO guidelines for the Programmatic Management of Drug-resistant Tuberculosis - Emergency update 2008

Glossary and abbreviations

Abbreviated New Drug Application (ANDA)
An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, 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 effectiveness. 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 to the American public[1].

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[2].

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

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

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

Ex works
A commercial term (incoterm) 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 quality risk of using antiretroviral, anti-TB and antimalarial products which are not yet WHO prequalified or authorised by a stringent regulatory authority, and to give advice to the Global Fund and the Global Drug Facility whether procurement of such products can be authorised.

Extensively drug-resistant TB
see XDR-TB

Extra-pulmonary TB
Form of TB where M. tuberculosis infect parts of the body other than the lungs. This is most commonly the lymph nodes, bones, central nervous system, cardiovascular and gastrointestinal systems.

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

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 approved by the Expert Review Panel also used by the Global Fund

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. To date, it has committed US$ 21.7 billion in 150 countries to support large-scale prevention, treatment and care programs against the three diseases[3].

Green Light Committee (GLC)
The GLC Initiative helps 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 consists 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).

Microscopy
Microscopy is currently the most commonly used technique to diagnose TB. Two to three sputum

1 http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#N)
2 QAS terminology database: http://www.who.int/medicines/services/expertcommittees/pharmprep/TermListcategory.pdf
3 WHO

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
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 effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to 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. For internal tracking purposes, all NDA's are assigned an NDA number[4].

Pharmacokinetic (PK)
The way the body affects the drug with time.

Pharmacodynamic (PD)
The effects of the drug on the body.

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 torsdes 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)

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. (as may be updated from time to time)[5].

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 Food and Drug Administration (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 PEPFAR programme[6].

WHO Prequalification (PQ)
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[7].

XDR-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.

4 http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#N
5 http://www.theglobalfund.org/documents/psm/List_of_Countries_SRA.pdf
6 QAS terminology database: http://www.who.int/medicines/services/expertcommittees/pharmprep/TermListcategory.pdf
7 WHO

References

1. Blanc L, Falzon D, Fitzpatrick C, Floyd K, Garcia I, Gilpin C, et al. Global tuberculosis control: WHO report 2010. [Online]. Geneva: World Health Organisation; 2010. [cited 2011 March 14]. Available from: http://whqlibdoc.who.int/publications/2010/9789241564069_eng.pdf

2. WHO. Tuberculosis. (Fact Sheet no. 104). [Online]. Geneva: World Health Organisation; 2010, November. [cited 2011, March 14]. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/

3. Falzon D, Glaziou P, Jaramillo E, Mirzayev F, Nathanson E, Sismanidis C, et al. Multidrug and extensively drug resistant TB (M/XDR-TB): 2010 global report on surveillance and response. [Online]. Geneva: World Health Organisation; 2010. [cited 2011 March 14]. Available from: http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf

4. Salmaan Keshavjee, M.D., Ph.D., and Paul E. Farmer, M.D., Ph.D. Picking Up the Pace - Scale-Up of MDR Tuberculosis Treatment Programs. [Online]. New England Journal of Medicine 2010 Nov 4; 363:1781-1784. [cited 2011, March 14]. Available from: http://www.nejm.org/doi/full/10.1056/NEJMp1010023

5. Stop TB Partnership. Road Map for MDR-TB scale up: The Global Drug Facility. [Online]. Stop TB Partnership, 2010, Nov. [cited 2011, March 14]. Available: http://www.stoptb.org/assets/documents/resources/publications/plan_strategy/GDF%20ROADMAP%20FOR%20MDR%20TB%202010%20Final.pdf

6. WHO. The Green Light Committee Initiative - frequently asked questions: What are the lead times for ordering second-line anti-TB drugs? [Online]. Geneva: World Health Organisation, . [cited 2011, March 14]. Available: http://www.who.int/tb/challenges/mdr/greenlightcommittee/faq8_lead_times/en/index.html

7. TB Alliance. Pathway to Patients: charting the dynamics of the global TB drug market - Compendium of findings. [Online]. TB Alliance, 2007, May. [cited 2011, March 14]. Available: http://www.tballiance.org/downloads/publications/Pathway_to_Patients_Compendium_FINAL.pdf

8. WHO. The Green Light Committee Initiative - frequently asked questions: How is the quality of second-line anti-TB drugs assured? [Online]. Geneva: World Health Organisation, . [cited 2011, March 14]. Available: http://www.who.int/tb/challenges/mdr/greenlightcommittee/faq9_quality_assurance/en/index.html

9. Salmaan Keshavjee, MD, Ph.D. Role of the Green Light Committee Initiative in MDR-TB Treatment Scale-up. [Online]. Proceedings of WHO presentation, 2009, April 3, Beijing. Geneva: World Health Organisation [cited 2011, March 14]. Available: http://www.who.int/tb_beijingmeeting/media/press_pack/presentations/day3_presentation4.pdf

10. World Lung Foundation. Tuberculosis: Global impact in The Acute Respiratory Infections Atlas, first edition. [Online]. 2010. World Lung Foundation. [cited 2011, March 15]. Available: http://www.ariatlas.org/tb_beijingmeeting/media/press_pack/presentations/day3_presentation4.pdf

11. Dalberg. Analysis of the 2nd line TB drugs market and the feasibility of advanced purchase commitments. 2010 November.

12. Sanchez-Padilla E, Dlamini T, Tefera Z.D, Ascorra A, Ruesch-Gerdes S, Calain P, et al. National survey on the prevalence of anti-tuberculosis drug resistance in the Kingdom of Swaziland. Epicentre, Paris, France; National Tuberculosis Control Program, Manzini, Swaziland; MSF-Switzerland, Genève, Switzerland; National Reference Center for Mycobacteria, Borstel, Germany. 2009.

13. Khan A. Stop TB Partnership: Draft Consensus Paper on New Framework for Supporting MDR-TB Scale Up. Email to Tido von Schoen-Angerer 2011, February 9 [cited 2011, March 21].

14. The Global Fund to Fight AIDS, Tuberculosis and Malaria. Lists of ARVs, TB and Malaria products. [Online]. 2011 [cited 2011, March 14]. Available at http://www.theglobalfund.org/en/procurement/list/?lang=en

15. Stop TB Partnership. Procurement and Supply. [Online] 2011 [cited 2011, March 14] Available at: http://www.stoptb.org/gdf/drugsupply/default.asp

16. UNITAID. MDR-TB Scale-up and Acceleration of Access.[Online] 2010. [cited 2011, March 14] Available at: http://www.unitaid.eu/en/mdr-tb-scale-up.html

17. Cambridge Economics Policy Associates (CEPA) LLP. Market Dynamics Study produced for the Global Fund to Fight AIDS, Tuberculosis and Malaria, Phase I Report. 2011 January 14.

18. Zhenkun M PhD, Lienhardt C PhD, McIlleron H PhD, Prof Nunn AJ MSc, Prof Wang X MD. Global tuberculosis drug development pipeline: the need and the reality. [Online] The Lancet, 2010 June 12, Vol 375 (9731): 2100 - 2109. [Published Online: 2010 May 19] Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60395-9/abstract

19. David McNeely and Andreas Diacon personal communication, IUATLD Conference, Berlin November 2010. Available at http://uwclh.conference2web.com/content/187

20. Christian Lienhardt personal communication, IUATLD Conference, Berlin November 2010. Available at http://uwclh.conference2web.com/content/391

21. Aït-Khaled N, Alarcón E, Armengol R, et al. Management of Tuberculosis: A Guide to the Essentials of Good Clinical Practice, sixth edition. [Online] The International Union Against Tuberculosis and Lung Disease. 2010, March. [cited 2011, March 14]. Available at: http://www.theunion.org/component/option,com_guide/Itemid,79/

22. WHO/Norwegian Institute for Public Health. ATC/DDD Index 2011. [Online] 2010, December 12 [cited 2011, March 14]. World Health Organisation Collaborating Centre for Drug Statistics Methodology. Available at: http://www.whocc.no/atc_ddd_index/

23. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008. [Online] 2008. [cited 2011, March 14]. World Health Organisation. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf

24. WHO. WHO Model List of Essential Medicines, 16th edition (updated). [Online]. 2010, March. [cited 2011, March 14] World Health Organisation. Available at:

http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf

25. WHO. WHO Model List of Essential Medicines for Children, 2nd edition (updated). [Online] 2010, March [cited 2011, March 11] World Health Organisation. Available at: http://www.who.int/medicines/publications/essentialmedicines/Updated_second_children_list_en.pdf

26. Harmon, F. Public letter on delayed supplies of kanamycin. [Online] 2009, February 25 [cited 2011, March 3]. APP Pharmaceuticals. Available at: http://www.apppharma.com/images/stories/appfiles/Kanamycin_Ltr_2_24_09_ltrhd.pdf

27. Gupta R, Kim J.Y, Espinal M.A, Caudron J-M, Pecoul, Farmer P.E, et al. Responding to Market Failures in Tuberculosis Control. [Online] Science, 2001, August 10: 1049-1051. Published online 2001, July 19 [cited 2011, March 10] Available at: http://www.sciencemag.org/content/293/5532/1049.summary?sid=296cc982-def8-4a77-b4ec-a7c4cc474993

28. Coyne K.M, Pozniak A.L, Lamorde M, Boffito M. Pharmacology of second-line antituberculosis drugs and potential for interactions with antiretroviral agents. [Online] AIDS. 2009, February 20, Vol 23 (4): 437-446 [cited 2011, March 16] Available at: http://journals.lww.com/aidsonline/fulltext/2009/02200/pharmacology_of_second_line_antituberculosis_drugs.1.aspx

29. British National Formulary. British National Formulary 60. Pharmaceutical Press. 2010, September 2010

30. Oanda.com GBP converted to USD [Online] [cited 2011, March 7] Available at www.oanda.com

31. Costello, I. British National Formulary for Children 2006, Cdr edition. Pharmaceutical Press. 2007, April 30

32. Stop TB Partnership. GDF product catalogue. [Online] 2011 [cited 2011, March 10] Available at: http://www.stoptb.org/gdf/drugsupply/drugs_available.asp

33. US FDA. Approved product label: USFDA Capastat. [Online] United States Food and Drug Administration. 2008, January 14. [cited 2011, March 15]. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

34. WHO. Global Price Reporting Mechanism. [Online] World Health Organisation. [cited 2011, March 10] Available at: http://apps.who.int/hiv/amds/price/hdd/index.aspx

35. US FDA. Highlights of prescribing information: Avelox. [Online] United States Food and Drug Administration. 2011, January. [cited 2011, March 9] Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021085s047,021277s041lbl.pdf

36. Rodríguez JC, Ruiz M, Climent A, Royo G. In vitro activity of four fluoroquinolones against Mycobacterium tuberculosis. [Online] Int J Antimicrob Agents. 2001, March 17 (3):229-31. [cited 2011, March 11] Available at: http://www.ncbi.nlm.nih.gov/pubmed/11282270

37. TB Alliance. TB Alliance Portfolio: Moxifloxacin. [Online] 2011, March. [cited 2011, March 15] Available at: http://www.tballiance.org/new/portfolio/html-portfolio-item.php?id=17

38. Hutchinson D.J, Johnson C.E, Klein K.C. Stability of extemporaneously prepared moxifloxacin oral suspensions. [Online] American Journal of Health-System Pharmacy. 2009, April 1, Vol. 66 (7): 665-667. [cited 2011, March 10] Available at: http://www.ajhp.org/content/66/7/665.abstract

39. VandenBussche H.L, Johnson C.E, Fontana E.M, Meram J.M. Stability of levofloxacin in an extemporaneously compounded oral liquid. [Online] American Journal of Health-System Pharmacy. 1999, Vol 56 (22) 2316-2318. [cited 2011, March 15] Available at: http://www.ajhp.org/content/56/22/2316.abstract?sid=f1807999-6f27-4f55-a74e-10700869f728

40. US FDA. Levofloxacin drud details. [Online] United States Food and Drug Administration.[cited 2011, March 7] Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

41. US FDA. Floxin Tablets (oxfloxacin tablets). [Online] United States Food and Drug Administration. 2008, September. [cited 2011, March 7] Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019735s059lbl.pdf

42. US FDA. Trecator (ethiomanide tablets, USP). [Online] United States Food and Drug Administration. 2005, December (revised) [cited 2011, March 10] Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/013026s024lbl.pdf

43. Wang F, Langley R, Gulten G, Dover LG, Besra GS, Jacobs WR Jr, et al. Mechanism of thioamide drug action against tuberculosis and leprosy. [Online] J Exp Med. 2007, January 22, Vol 204 (1): 73-8. Published online 2007, January 16 [cited 2011, March 8] Available at: http://www.ncbi.nlm.nih.gov/pubmed/17227913

44. Drugs.com. Kantrex official FDA information, side effects and uses. [Online] 2006, March [cited 2011, March 7] Available at: http://www.drugs.com/pro/kantrex.html

45. US FDA. Amikacin overview. [Online]. [cited 2011, January 4] Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=AMIKACIN%20SULFATE

46. Drugs.com. Amikacin official FDA information, side effects and uses. [Online] 2007, December. [cited 2011, March 15] Available at http://www.drugs.com/pro/amikacin.html

47. Green Light Committee Initiative. Annual Report 2008. [Online] World Health Organisation/Stop TB Partnership. 2009 [cited 2011, March 21]. Available at http://whqlibdoc.who.int/hq/2009/WHO_HTM_TB_2009.421_eng.pdf

48. TDR. Childhood tuberculosis: addressing a forgotten crisis. [Online] UNICEF/UNDP/World Bank/WHO. 2011, January 11 [cited 2011, March 16] Available at: http://apps.who.int/tdr/svc/news-events/news/paediatric-tb

49. Médecins Sans Frontières. Scaling-Up Diagnosis Treatment of Drug-Resistant Tuberculosis in Khayelitsha: An Integrated, Community-based Approach. [Online] March 2011 [cited 2011, March 21] Available at http://www.msf.org.za

50. Axel A, Dr. Personal Communication with Karen Day. [E-mail]. 2011, March 11

51. HIV Drug Interactions. Drug Interaction charts - interactions with anti-HIV and other drugs. [Online] The University of Liverpool. 2010 [cited 2011, March 18] Available at: http://www.hiv-druginteractions.org/Interactions.aspx

52. Axel A, Dr. Petha: Summary of Product Characteristics, Revision Dec 2008 (English Translation supplied by Fatol). Personal communication with Karen Day. [E-mail] 2011, March 9.

53. The Chao Center. Seromycin; Cycloserine capsules USP. [Online] 2005, April 28 (revised) [cited 2011, March 18] Available at: http://www.thechaocenter.com/seromycin/product_insert.pdf

54. Axel A, Dr. Terizidon: Summary of Product Characteristics, Revision Dec 2009 (English Translation supplied by Fatol). Personal communication with Karen Day. [E-mail] 2011, March 11.

55. US FDA. Paser drug details. [Online] United States Food and Drug Administration. [cited 2011, March 18] Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

56. Sweetman, S.C. Martindale Complete Drug Reference Guide, 33rd Edition. Pharmaceutical Press, 2002. pp148-3

57. US FDA. Lamprene drug details. [Online] United States Food and Drug Administration. 2002, July (revised) [cited 2011, March 18] Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

58. Novartis. Lamprene pricing info. [Online] Pharmaworld.com. 2007 [Cited 2011, March 18]. Available at: http://www.lamprene.com/index.php?id=4

59. US FDA. Linezolid drug details. [Online] United States Food and Drug Administration. [cited 2011, March 18] Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=LINEZOLID

60. US FDA. Zyvox drug details. [Online] United States Food and Drug Administration. 2010, June (revised) [cited 2011, March 18] Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

61. Espacenet. Substituted oxazine and thiazine oxazolidinone antimicrobials. [Online] European Patent Office. [cited 2011, March 22] Available at: http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_EP&FT=D&date=19950316&CC=WO&NR=9507271A1&KC=A1

62. Espacenet. Linezolid-crystal form II. [Online] European Patent Office. [cited 2011, March 22] Available at: http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_EP&FT=D&date=20010809&CC=WO&NR=0157035A1&KC=A1

63. Espacenet. Oxazolidinone tablet formulation. [Online] European Patent Office. [cited 2011, March 22] Available at: http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_EP&FT=D&date=20010927&CC=WO&NR=0170225A2&KC=A2

64. The Global Fund. Price and quality reporting. [Online] 2011 [cited 2011, March 16] Available at: http://www.theglobalfund.org/en/procurement/pqr/

65. Espacenet. Benzoxazine derivatives. [Online] European Patent Office. [cited 2011, March 22] Available at: http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&at=24&locale=en_EP&FT=D&CC=US&NR=4382892A&KC=A

66. Espacenet. Optically active pyridobenzoxazine derivatives and anti-microbial use. [Online] European Patent Office. [cited 2011, March 22] Available at:http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&at=26&locale=en_EP&FT=D&CC=US&NR=5053407A&KC=A

67. Erturan Z, Uzun M..In vitro activity of linezolid against multidrug-resistant Mycobacterium tuberculosis isolates. Expe Int J Antimicrob Agents. 2005 July, Vol 26 (1):78-80

68. Working group on new TB drugs. Pipeline : View by phase. [Online] [cited 2011 March 14] Available from: http://www.newtbdrugs.org/pipeline.php

69. TB Alliance. More than ever: 2010 Annual report. [Online] 2010. Available from: http://www.tballiance.org/downloads/publications/TBA021_AR2010.pdf

70. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS 2001;15:143-52.

71. US FDA. Drug product details. [Online] United States Food and Drug Administration. [cited 2011, March 7] Available at: http://www.accessdata.fda.gov scripts/cder/drugsatfda/index.cfm

72. WHO. Towards Universal Access to Diagnosis and Treatment of Multi-Drug-Resistant and Extensively Drug-Resistant Tuberculosis by 2015. WHO Progress Report. Publication pending 2011.

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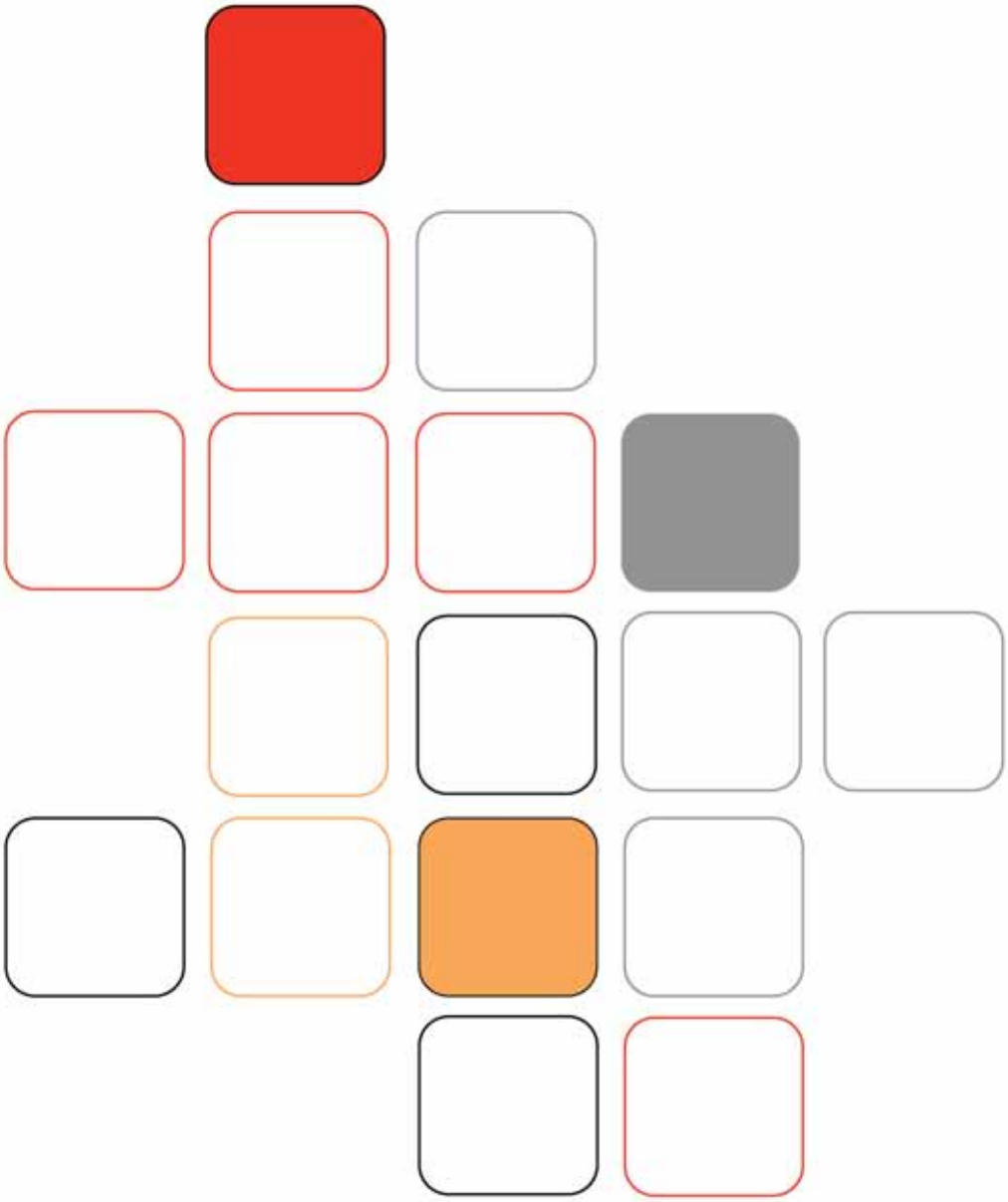
DISCLAIMER

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 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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