DR-TB DRUGS UNDER THE MICROSCOPE

5th Edition (Abridged)

ONLINE SUPPLEMENT

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The 5th edition of "DR-TB Drugs Under the Microscope" chronicles the changing landscape of available treatments for DR-TB, outlines the key barriers to accessing the most effective treatments, and makes recommendations for action that can improve TB care on a global scale. The full issue brief is available at www.msfaccess.org/utm5.

This Online Supplement to "DR-TB Drugs Under the Microscope" includes additional information on drug prices and quality, registration status, and paediatric formulations available to treat children with DR-TB. Company contacts and conditions of offer are also presented.

DRUG PRICE AND QUALITY INFORMATION

Based on information collected from companies up to July 2018.

METHODOLOGY

The table below presents the sources and prices of five key anti-tuberculosis medicines from Group A (bedaquiline, linezolid), Group B (clofazimine) and Group C (delamanid, imipenem-cilastatin) used to build DR-TB regimens as classified in the World Health Organization (WHO) Rapid Communication dated August 2018[1].

DATA COLLECTION

To collect information on price, questionnaires were sent to companies listed on the Global Fund List of Tuberculosis Pharmaceutical Products[2] that:

- manufacture at least one of the following drugs: linezolid, clofazimine, imipenem-cilastatin, bedaquiline and delamanid, and
- are either (i) listed on the WHO List of Prequalified Medicinal Products, (ii) approved by a stringent drug regulatory authority (SDRA), or (iii) temporarily approved by the Global Fund/Global Drug Facility (GDF) Expert Review Panel (ERP).

The data were collected up to July 2018.

PRICE INFORMATION

Prices are listed where manufacturers agreed to share information. A number of manufacturers did not share information:

- Fresenius Kabi did not wish to contribute to the publication.
- Demo, Novartis, Pfizer, Sandoz and Teva did not agree to publish prices.
- PanMedica/Panpharma did not answer our messages.

Prices are given in US dollars (US$), rounded up to the nearest third decimal point, and correspond to the lowest unit price (i.e. the price of one tablet, capsule or vial). When prices that varied according to packaging (e.g. blisters or bottle) were received from a manufacturer for the same formulation, the lowest price was selected. Prices listed are 'ex works' except for prices provided by Macleods (FOB) and by Sun Pharma (DAP Merignac or DAP Brussels). Please see noted reference for an explanation of these incoterms[3].

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

Prices offered by the Stop TB Partnership/GDF pooled procurement mechanism are also 'ex works' and correspond to the lowest and highest prices referenced per medicine on the GDF website[4]. Note that prices in the GDF price catalogue can fluctuate during the year if, for example, a long-term agreement with different suppliers comes to an end. A range of prices is provided per medicine without specific figures per manufacturer.

QUALITY INFORMATION

Products that are either listed on the WHO List of Prequalified Medicinal Products or approved by an SDRA are listed in the price tables as 'approved'. Products that are undergoing review by either WHO Prequalification or an SDRA, or that have been reviewed and listed by the Global Fund/GDF ERP, are listed in the price tables as 'under evaluation'. Products that have not yet been submitted to WHO Prequalification or to an SDRA have not been included. Submissions to WHO Prequalification are confidential and all companies mentioned that have a dossier accepted for review have given MSF the permission to disclose this information. As the information on the WHO List of Prequalified Medicinal Products is updated regularly, the list should be consulted for up-to-date information[5].

Products procured by GDF comply with the GDF's Quality Assurance Policy[6]. This deems eligible for GDF procurement all products that are included on the WHO List of Prequalified Medicinal Products, approved by an SDRA, or approved by the joint Global Fund/GDF ERP. The ERP is an independent technical body whose purpose is to review the potential quality risk of using medicines which are not yet WHO prequalified or authorised by an SDRA, and to give advice to the Global Fund and GDF as to whether time-limited procurement of such products can be authorised. The list of ERP-reviewed products for tuberculosis can be consulted on the Global Fund website[7].

[1] http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf
[2] https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf?u=636669192690000000
[3] https://iccwbo.org/resources-for-business/incoterms-rules/incoterms-rules-2010/
[4] http://www.stoptb.org/gdf/drugsupply/pc2.asp?CLevel=1&CParent=1
[5] https://extranet.who.int/prequal/content/prequalified-lists/medicines
[6] http://www.stoptb.org/gdf/drugsupply/quality_sourcing_process.asp
[7] https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/

BEDAQUILINE (BDQ)

	Johnson & Johnson	Pharmstandard	GDF pooled procurement
Quality	**SDRA approved***	**Under SDRA evaluation**	**GDF Quality Assurance Policy**
50mg film coated tablet	**2.127†**	**8.420**	**0.000 (donation until March 2019)**

* Bedaquiline received US FDA accelerated approval on the basis of phase IIb clinical trial data.
† For South Africa. Also for National TB Programmes procuring via the Global Drug Facility (GDF); all other entities should contact the GDF directly.

DELAMANID (DLM)

	Otsuka	GDF pooled procurement
Quality	**SDRA approved and under evaluation with WHO PQ**	**GDF Quality Assurance Policy**
50mg film coated tablet	**2.530**	**2.530**

CLOFAZIMINE (CFZ)

	Novartis	Macleods	GDF pooled procurement
Quality	**SDRA approved**	**Under evaluation by WHO PQ**	**GDF Quality Assurance Policy**
50mg soft-gel capsule	**Manufacturer did not agree to publish prices**	**xx**	**NA**
100mg soft-gel capsule	**Manufacturer did not agree to publish prices**	**xx**	**0.982**
50mg tablet	**xx**	**Under evaluation by WHO PQ**	**NA**
100mg tablet	**xx**	**Under evaluation by WHO PQ**	**NA**

LINEZOLID (LZD)

	Cipla	Dr Reddy's	Hetero	Macleods	Pfizer	Sandoz	Teva	GDF pooled procurement
Quality	**WHO PQ & SDRA approved**	**SDRA approved**	**WHO PQ & SDRA approved**	**WHO PQ**	**SDRA approved**	**SDRA approved**	**SDRA approved**	**GDF Quality Assurance Policy**
600mg tablet	**1.379**	**2.930**	**1.500**	**1.000***	**Manufacturer did not agree to publish prices**	**Manufacturer did not agree to publish prices**	**Manufacturer did not agree to publish prices**	**0.970-1.400**
100mg/ml powder for suspension	**xx**	**xx**	**xx**	**xx**	**Manufacturer did not agree to publish prices**	**xx**	**xx**	

* 'Free on Board' (FOB) price

IMIPENEM-CILASTATIN (IPM-CS)

	DEMO	Fresenius Kabi	Labatec	Sun Pharma	GDF pooled procurement
Quality	**SDRA approved**	**SDRA approved**	**SDRA approved**	**SDRA approved**	**GDF Quality Assurance Policy**
500mg + 500mg, powder for injection	**Manufacturer did not agree to publish prices**	**Manufacturer did not agree to publish prices**	**12.5**	**3.840***	**3.100-3.600**

* 'Delivered at Place' (DAP) Merignac or DAP Brussels price

DRUG REGISTRATION STATUS

Based on information collected from companies up to July 2018.

METHODOLOGY

The table below presents the sources and regulatory status of five key anti-tuberculosis medicines from Group A (bedaquiline, linezolid), Group B (clofazimine) and Group C (delamanid, imipenem-cilastatin) used to build DR-TB regimens as classified in the World Health Organization (WHO) Rapid Communication dated August 2018[8].

DATA COLLECTION

To collect data on regulatory status, questionnaires were sent to companies listed on the Global Fund List of Tuberculosis Pharmaceutical Products[9] that manufacture linezolid, clofazimine, imipenem-cilastatin, bedaquiline or delamanid, and that are listed on the WHO List of Prequalified Medicinal Products, approved by a stringent drug regulatory authority (SDRA), or temporarily approved by the Expert Review Panel (ERP) of the Global Fund. The data were collected up to July 2018.

REGULATORY STATUS INFORMATION

Manufacturers were asked to specify the regulatory status of their compounds according to their:

- **Registration status at SDRAs**, defined as: "(a) a member of the International Conference of Harmonisation (ICH[10]); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and WHO; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein."
- **Registration status in TB and DR-TB high-burden countries (HBC)[11]**, including:
  - TB HBC (30): Angola, Bangladesh, Brazil, Cambodia, Central African Rep, China, Congo, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Russian Federation, Sierra Leone, South Africa, Tanzania, Thailand, Vietnam, Zambia, Zimbabwe
  - DR-TB HBC (30): Angola, Azerbaijan, Bangladesh, Belarus, China, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Pakistan, Peru, Papua New Guinea, Philippines, Rep. Moldova, Russian Federation, Somalia, South Africa, Tajikistan, Thailand, Ukraine, Uzbekistan, Vietnam, Zimbabwe

[8] http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf
[9] https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf?u=636669192690000000
[10] http://www.ich.org
[11] As defined by the World Health Organization and Stop TB Partnership: http://www.stoptb.org/countries/tbdata.asp

Drug name	Company	Stringent regulatory agencies		TB or DR-TB high-burden countries*	
		Registered in	Under evaluation in	Registered in	Under evaluation in
		Countries where the product is registered	*Countries where the product has been submitted for registration*	*Countries where the product is registered*	*Countries where the product has been submitted for registration*
Clofazimine (CFZ)					
50mg soft-gel capsule	Novartis	Switzerland (leprosy indication)	Switzerland (TB indication)	None (TB indication)	South Africa (TB indication)
100mg soft-gel capsule	Novartis	Switzerland (leprosy indication)	Switzerland (TB indication)	None (TB indication)	South Africa (TB indication)
50mg tablet	Macleods†	None	None	None	None
100mg tablet	Macleods†	None	Unknown	None	Unknown
Linezolid (LZD)					
600mg tablet	Cipla	Australia	New Zealand	India, Kenya, Mozambique, Tanzania	Nigeria, Peru, Philippines, Zimbabwe
	Dr Reddy's	Germany, UK	None	None	None
	Hetero	EU, USA	None	Ethiopia, India, Kenya, Mozambique, Peru, Zimbabwe, Namibia, Zambia, South Africa	Kazakhstan, Kyrgyzstan, Myanmar, Thailand, Vietnam
	Macleods	None	None	Cambodia, Ethiopia, Kenya, Mozambique, Myanmar, Tanzania, Vietnam, Zimbabwe	Nigeria, Philippines, Zambia
	Sandoz	Canada, Switzerland	None	None	Philippines, South Africa
	Teva	Austria, Croatia, Denmark, Italy, Germany, Netherlands, Portugal, Spain, Sweden	None	None	None
100mg/5ml powder for suspension	Pfizer	UK	Unknown	Unknown	Unknown
Imipenem-cilastatin (IPM-CS)					
500mg/500mg powder for injection	Labatec	Switzerland	None	None	None
	Sun Pharma	France	None	Brazil, China, Congo, DR Congo, Kenya, Kyrgyzstan, Mozambique, Myanmar, Moldova, South Africa, Tajikistan, Tanzania, Thailand, Ukraine, Vietnam, Zambia, Zimbabwe	Cambodia, Nigeria, Peru
Delamanid (DLM)					
50mg tablet	Mylan, Otsuka, R Pharm	EU, Japan	None	China, India, Philippines,	Indonesia, Peru, Russian Federation, South Africa, Ukraine
Bedaquiline (BDQ)					
100mg tablet	Johnson & Johnson, Pharmstandard	EU, USA, Japan, Iceland, Norway, Lichtenstein	None	China, Ethiopia, India, Indonesia, Moldova, Peru, Philippines, Russian Federation, South Africa, Thailand, Ukraine, Uzbekistan	Bangladesh, Belarus, Brazil, Kenya, Myanmar, Nigeria, Tanzania, Vietnam, Kazakhstan

* TB and DR-TB high burden countries (HBC):
TB HBC (30): Angola, Bangladesh, Brazil, Cambodia, Central African Rep, China, Congo, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Russian Federation, Sierra Leone, South Africa, Tanzania, Thailand, Vietnam, Zambia, Zimbabwe
DR-TB HBC (30): Angola, Azerbaijan, Bangladesh, Belarus, China, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Mozambique, Myanmar, Nigeria, Pakistan, Peru, Papua New Guinea, Philippines, Rep. Moldova, Russian Federation, Somalia, South Africa, Tajikistan, Thailand, Ukraine, Uzbekistan, Vietnam, Zimbabwe

† Macleods was granted Global Fund/Global Drug Facility Expert Review Panel status for CFZ 50mg tablet and CFZ 100mg tablet but the company has not yet communicated on the registration process.

PAEDIATRIC FORMULATIONS AVAILABLE TO TREAT CHILDREN WITH DR-TB

Products in the table below are either WHO-prequalified or have Global Drug Facility/Global Fund Expert Review Panel status (as of September 2018)

Drug name	Company	Quality status*,†	
Moxifloxacin hydrochloride, equivalent to 100mg base, dispersible tablet	Macleods	ERP	ERP status valid 1 year until July 2019
	Micro Labs	ERP	ERP status valid 1 year until July 2019
Cycloserine 125mg capsule	Macleods	WHO PQ	Since July 2018
Levofloxacin 100mg dispersible tablet	Macleods	WHO PQ	Since February 2018
	Micro Labs	ERP	ERP status valid 1 year until July 2019
Ethionamide 125mg dispersible tablet	Macleods	WHO PQ	Since May 2017
	Micro Labs	ERP	ERP status valid 1 year until July 2019
Pyrazinamide 150mg dispersible tablet	Macleods	WHO PQ	Since December 2016
	Micro Labs	WHO PQ	Since September 2017
Isoniazid 100mg breakable tablet	5 generics manufacturers	WHO PQ	Since 2008

* https://extranet.who.int/prequal/content/prequalified-lists/medicines
† https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf?u=636669192690000000

CONDITIONS OF OFFER, AS QUOTED BY COMPANIES

Definitions of eligibility vary from company to company. The conditions detailed in the table below are those quoted by companies and collected up to July 2018.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods*
Cipla				Ex works
Dr Reddy's	No restriction	No restriction		Ex works UK
Hetero	Prices indicated are available for all generic accessible countries and/or the countries where there are no patent restrictions. Additionally, products which are manufactured under license from the originator will be available for sale to countries within the list of agreed territory	Prices indicated are applicable for public procurement programmes and for not-for-profit organisations under the access programme of the company.		Ex works Hyderabad
Johnson & Johnson	Countries purchasing through the Global Drug Facility (contact GDF for full details) and South Africa	National TB programmes via the Global Drug Facility; all other entities should contact the Global Drug Facility directly. Manufacturer makes Sirturo available in all other countries directly via its local affiliates.	There is an ongoing donation programme via USAID/GDF for more than 100 eligible countries until March 2019.	Ex works
Labatec	All	All		Ex works
Macleods	No restriction	No restriction		FOB
Novartis				Ex works
Otsuka	Price indicated is for Global Fund eligible countries that procure via the Global Drug Facility. Prices in other countries may vary.	NGOs and global health institutions that procure product via the Global Drug Facility.		Ex works
Pharmstandard	Price indicated is available for CIS countries and Georgia.	Price indicated is available for TB hospitals, TB institutes and specific TB medical organisations		Ex works
Sandoz				Ex works
Sun Pharma	No restriction	No restriction	All demands have to be sent to Mr Yohan Penven: yohan.penven@sunpharma.com	DAP Merignac or DAP Brussels
Teva				Ex works

* For an explanation of incoterms in this column, please see: https://iccwbo.org/resources-for-business/incoterms-rules/incoterms-rules-2010/

COMPANY CONTACTS

Company	Contact name	Title	Company's address	Telephone number	E-mail address
Cipla	Mr Sharadd Jain	Vice President, Cipla Global Access	Cipla House, Peninsula Business Park Ganpatrao Kadam Marg, Lower Parel Mumbai 400 013, Maharashtra India	+91 22-24826000	sharadd.jain@cipla.com; nisha.dolas@cipla.com
Dr Reddy's	Mr Ganesh Venkatraman	Associate Director, Business Development	8-2-337, Road No. 3 Banjara Hills, Hyderabad, Telangana 500034 India	+44 7827157230	gvenkataraman@drreddys.com
Hetero	Mr Rahul Lande	Associate Vice President, International Business	607/608, Matharu Arcasde, Plot No. 32 Subhash Road, Vile Parle (East) Mumbai - 400 057 India	+91 22 6691 0809	rahul.lande@heterodrugs.com
Johnson & Johnson	Mrs Ana-Maria Ionescu	Global Access Leader, TB	One Johnson & Johnson Plaza New Brunswick, New Jersey 08933 USA	+1 (732) 524-0400	aionescu@its.jnj.com
Labatec	Mrs Muriel Xatard	Supply Chain Director	10, route de l'Aeroport WTC-1, 2nd Floor CH-1215 Meyrin (GE) Switzerland	+41 22 785 95 00	muriel.xatard@labatec.com
Macleods	Mr Vijay Agarwal; Mrs Rohini Karde; Mrs Niti Desai	Vijay Agarwal: Business Development Director Rohini Karde: Manager Institutional Business Niti Desai: Institutional Business	304, Atlanta Arcade Marol Church Road, opposite Leela hotel Andheri-kurla road, Andheri(east) Mumbai 400059 India	+91 22-66762800	vijay@macleodspharma.com; rohinik@macleodspharma.com; nitid@macleodspharma.com
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