

To: Dr. JC Gouws
Registrar of Medicines
Private Bag x 828
Pretoria
0001

RE: Urgent need to register quality generic versions of linezolid in South Africa

23 November 2015

Dear Dr. Gouws:

This letter follows from a communication with the Office of the Registrar on October 30, 2014, in which over 100 clinicians and healthcare workers, patients with drug-resistant tuberculosis (DR-TB), and civil society organizations urged the Medicines Control Council (MCC) to assess as a matter of priority the dossiers of generic companies submitting for registration of the medicine, linezolid.¹ This letter is attached as Annex 1. **We are now writing to reiterate the importance of urgently registering further quality generic versions of linezolid in South Africa, in order to improve its availability as a part of treatment regimens for patients with DR-TB.**

The October 2014 letter to the Registrar noted the high price of linezolid as a critical barrier to access, limiting the ability of clinicians across the country to include it in regimens for DR-TB patients. At the time, only a single supplier of linezolid—pharmaceutical company, Pfizer— was registered in South Africa and selling their product in the private sector at the prohibitive price of more than R700 per 600mg tablet.²

The letter's signatories were of the view that registration of further quality-assured suppliers would bring down the price of linezolid, to the point where the National Dept. of Health (NDOH) could purchase the medicine on tender and make it nationally available in the public sector to DR-TB patients in need. The MCC subsequently registered a generic linezolid dossier from Hetero, which is currently being marketed in South Africa by Sanofi. We commend the MCC for registration of a second linezolid supplier; however, it has unfortunately not been enough to facilitate adequate price reductions. Today, Pfizer markets linezolid in the private sector for over R875 per tablet, while Hetero linezolid costs over R655 per tablet.³ Greater competition is required to reduce prices to affordable levels.

In June 2014, the international medical humanitarian organization, Doctors Without Borders (MSF), received authorization from the MCC to import generic linezolid manufactured by Hetero which, at that time, was unregistered in South Africa but approved by a stringent regulatory authority.⁴ This product was purchased by MSF at an 88% discount on the South African private sector price, but was limited to use in MSF operations in Khayelitsha sub-district of the Western Cape. Prior to this authorization, MSF was purchasing Pfizer linezolid on the private market, and initiating one to four DR-TB patients per month on treatment regimens containing linezolid. Once MSF was authorized to use the more affordable product, the number of DR-TB patients initiated on linezolid-containing regimens every month in Khayelitsha increased and more than doubled in some instances, with up to nine patients a month being initiated (See Annex 2). Availability of the cheaper generic meant that MSF no longer felt constrained to

¹<http://www.treatmentactiongroup.org/sites/g/files/g450272/f/201411/MCC%20linezolid%20letter.pdf>

²<http://www.msfacecess.org/content/linezolid-fact-sheet-0>

³<http://mpr.code4sa.org/#search:linezolid>

⁴<http://www.msfacecess.org/content/linezolid-fact-sheet-0>

limit provision of linezolid to just a fraction of patients who had run out of adequate treatment options but could instead offer it to all of those in need.

While MSF continues to access Hetero's generic product for use in Khayelitsha through its own supply channels, the NDOH has been unable to secure an affordable bid for linezolid tablets through the anti-infectives tender. The NDOH requested bids to supply 114,500 units of 10x 600mg tablet packs of linezolid between October 1, 2015 and September 30, 2017⁵—enough supply to provide a six-month course of linezolid to the targeted 3,000 DR-TB patients per year.⁶⁷ However, no successful bidders for linezolid tablets were listed on the subsequent contractual agreements.⁸ South Africa's tender is, to our knowledge, one of the largest requests for linezolid made by a national government. As patients' outcomes could benefit from taking linezolid for longer than six months—ranging up to the full two years of treatment—and lower prices could result in NDOH expanding linezolid eligibility to include even more of the country's confirmed cases of DR-TB (18,734 patients in 2014⁹), the potential market for linezolid in South Africa is even larger than the current request.

Had supply been obtained through the tender, linezolid would be more readily available in the public sector. Instead, provinces wishing to use linezolid for DR-TB must purchase it through a buy-out, directly from pharmaceutical companies. The current cost per patient to MSF for a six-month supply of Hetero linezolid is approximately ~R20,000 (~R109/tablet), inclusive of import duties and VAT. In June 2015, however, Sanofi provided a quote to the Provincial Government of the Western Cape (PGWC) for the Hetero product that it markets, at a price of ~R29,000 per six-month supply (~R159 per tablet). Pfizer's offer to PGWC was ~R39,000 per six-month supply (~R214 per tablet).¹⁰ While lower than private sector costs, the prices offered by Sanofi and Pfizer are too high, and will limit both the number of DR-TB patients to whom linezolid can be offered in the public sector, as well as the duration of treatment on linezolid for those who do receive it. In some cases, facilities or provinces may be choosing not to access linezolid at all due to budgetary constraints, leaving patients with the options of either foregoing this life-saving medication or purchasing it in the private sector. See Annex 3 for current linezolid prices.

Countries like South Africa, which benefit from Global Fund support, should be paying prices on par with the Global Drug Facility, which is the supply channel for the Global Fund. At present, the Global Drug Facility price for linezolid currently stands at between 5.35 and 5.48 USD per 600 mg tablet¹¹ (~R76)¹². A study recently presented at the 15th European AIDS conference indicated that the cost of production of treatments for MDR-TB was at least 80-85% lower than the current prices charged by manufacturers and that the target price achievable for linezolid *per month* is 4.90-12.80 USD¹³. It is clear that current prices being offered to South Africa are unreasonably high.

⁵<http://www.health.gov.za/tender/docs/tenders/HP022015AI01Bid.pdf>

⁶<http://www.health-e.org.za/2015/06/11/more-than-r130-million-slated-for-new-tb-drugs/>

⁷ This calculation is based on a DR-TB patient taking one 600mg tablet per day for a total of six months (182 tablets in total). However, some patients' outcomes could benefit from taking linezolid for a longer period of time—ranging up to the full two-year duration of DR-TB treatment. As linezolid is indicated for infections other than TB, it is assumed the excess number of tablets (beyond what is required for a six-month supply for 3,000 DR-TB patients per year) would be used for treating patients with these other conditions.

⁸<http://www.health.gov.za/tender/docs/contracts/HP022015AICC.pdf>

⁹https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryPr ofile&ISO2=ZA&LAN=EN&outtype=html

¹⁰ Communication between MSF and PGWC.

¹¹<http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=818>

¹² Exchange rates as of October 29, 2015 on <http://www.xe.com/currencyconverter/>

¹³Gotham D et al. *Target generic prices for novel treatments for drug-resistant tuberculosis*. 15th European AIDS Conference, Barcelona, abstract PS2/4, 2015.

The current state of linezolid access in South Africa is not acceptable, given the right enshrined in section 27 of the country's constitution, to have access to health care services.¹⁴ However, options exist for the state to comply with its constitutional obligation to "take reasonable legislative and other measures, within its available resources, to achieve the progressive realization" of this right—namely, rapid registration of further linezolid suppliers. There is robust evidence suggesting that drug prices drop precipitously as more generic manufacturers enter the market,¹⁵ and as evidenced by MSF experience in Khayelitsha, price reductions would significantly improve clinicians' ability to access and prescribe linezolid for patients in need.

A number of pharmaceutical companies currently produce linezolid, and Teva, Mylan, Glenmark, Gate, and Amneal all have tentative approval¹⁶ from the United States Food and Drug Administration, which is recognized as a stringent regulatory authority. We are aware that some of these suppliers have already applied, or intend to apply for registration of linezolid in South Africa. Rapid registration of additional suppliers' quality generic versions of linezolid would facilitate a more competitive tender process, and improve the likelihood of success for the NDOH to reach its target of initiating 3,000 patients a year on linezolid-containing regimens, with a view to increase that number in subsequent years. At present, this goal will not be realized, primarily due to the inability to access an affordable product.

Tuberculosis in general and the growing DR-TB epidemic in particular remain some of the biggest threats to the health of the South African citizenry.^{17,18} Linezolid is increasingly recognized in international forums as a crucial component of robust DR-TB regimens, as evidenced both by systematic reviews¹⁹, and its recent inclusion on the World Health Organization's Essential Medicines List.^{20,21} A lack of access to linezolid means that some patients are prescribed regimens for DR-TB that are less robust than if linezolid were available. This potentially leads to amplification of drug resistance and transmission of drug-resistant strains of TB, potentially exacerbating the DR-TB epidemic in South Africa.

Linezolid is recommended by NDOH as a treatment for DR-TB in certain instances, if cost permits²². At present, cost does not permit—linezolid is one of the most expensive of many costly medicines in South Africa included in an effective multi-drug regimen for treating DR-TB.²³ However, with the leadership of the MCC in registering additional generic suppliers, access for clinicians and their DR-TB patients to more affordable linezolid, and improved outcomes for DR-TB patients, could become a reality in South Africa.

We urge the MCC to take expedient action to remedy the lack of access to affordable quality-assured linezolid for treating DR-TB, and request the MCC provide timely updates on newly registered linezolid suppliers to these signatories, via msfocb-capetown-deputyhom@brussels.msf.org

¹⁴<http://www.gov.za/documents/constitution/chapter-2-bill-rights#27>

¹⁵<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm>

¹⁶FDA reviews the marketing applications using its normal standards for authorization. If the product still has marketing protection in the U.S., FDA issues a "tentative approval" rather than a "full" approval. The "tentative" approval signifies that the product meets all safety, efficacy, and manufacturing quality standards for marketing in the U.S., and, but for the legal market protection, it would be on the U.S. market.

¹⁷<http://www.statssa.gov.za/publications/P03093/P030932013.pdf>

¹⁸<http://www.msf.org/international-activity-report-2011-south-africa>

¹⁹<http://www.treatmentactiongroup.org/tb/linezolid-factsheet> and <http://erj.ersjournals.com/content/40/6/1430.abstract>

²⁰http://www.who.int/tb/features_archive/essential_medicines_2015/en/

²¹<http://www.treatmentactiongroup.org/tb/linezolid-factsheet> and <http://www.ncbi.nlm.nih.gov/pubmed/22325685> and <http://www.nejm.org/doi/full/10.1056/NEJMoa1201964>

²²<http://www.hst.org.za/sites/default/files/TBpolicy.pdf>

²³<http://www.msfacecess.org/content/linezolid-fact-sheet-0>

Sincerely,

Organizations:



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Heena Narotam
TB Proof

Pat Bond
MDR TB survivor

Dr Yolande Theron
Medical Officer
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Dr Carol Cragg
HIV/TB Programme manager
Khayelitsha/Eastern substructure

**The following signatory was added to the letter following its delivery to the MCC:*

Dr Nesri Padayatchi
Deputy Director
CAPRISA

Annex 1:

To: Ms. Mandisa Hela
The Registrar of Medicines
Medicines Control Council
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Pretoria 0001
Per email: helam@health.gov.za
Per fax: +27 12 395 9201

30 October 2014

Dear Ms. Hela:

We, the undersigned clinicians, health care providers, DR-TB patients, and civil society organisations, commend the Medicines Control Council (MCC) on its June 26th, 2014 decision, granting Doctors Without Borders (MSF) authorisation to use a generic linezolid product in treatment regimens for selected patients with drug-resistant tuberculosis (DR-TB) in Khayelitsha, Western Cape¹. This is an important first step toward expanding access to linezolid for DR-TB patients in South Africa. However, **we urge the MCC to immediately register the same generic linezolid product currently under a fast-track review, in order to ensure linezolid is available for all DR-TB patients in need across the country.**

The MSF application under section 21 of the *Medicines and Related Substances Act 101 of 1965* (“the Act”) was based on the unaffordability of the brand name product, Zyvoxid. Prior to the MCC authorisation, MSF purchased Zyvoxid at the exorbitant private sector price of over R700 per 600mg tablet. The cost of this single drug consumed over 10% of the annual MSF operational budget for HIV and TB programmes in Khayelitsha, limiting the number of patients to whom linezolid could be offered. The generic product from manufacturer, Hetero, is purchased by MSF at less than R80 per tablet—a price reduction of over 88%—and provided in terms of the section 21 authorisation from the MCC. Other clinicians in South Africa are also struggling to offer linezolid to all patients who might benefit from the drug’s use, due to the unaffordability of Zyvoxid. Patients who must access Zyvoxid through the private sector are finding it is not covered by their medical aid due to the high cost, and they cannot afford it on an out-of-pocket basis.²

The MCC granted MSF section 21 authorisation after confirming the Hetero product’s approval by the United Kingdom’s Medicines and Healthcare Products Regulatory Agency (MHRA)—a stringent drug regulatory authority and fellow member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The same product dossier was submitted to the MCC for full registration in South Africa on the 29 April 2013, and granted fast-track approval status on 6 June 2013. Hetero made a full submission in this regard to the MCC on the 12 June 2013, after which the MCC should have supplied a decision within nine months, in line with Regulation 5 of the General Regulations made in terms of the Act. Over 16 months have now passed, with no decision concerning the application for registration reaching Hetero, to our knowledge.

¹ <https://www.msf.org.za/msf-publications/more-msf-patients-with-dr-tb-gain-access-to-dramatically-cheaper-version-life>

² <http://www.health-e.org.za/2014/10/03/xdr-tb-patients-smuggle-pills-treatment-priced-reach/>

It is unclear to the parties signing this letter why the MCC deems the generic product of sufficient quality for MSF to use, but has not yet fully registered the drug. Full registration of one or more quality generics would allow the National Department of Health to open a more competitive tender and obtain a more affordable linezolid product to address the huge public health impacts of the TB epidemic. It would allow clinicians across South Africa to have fewer concerns for cost when prescribing linezolid to DR-TB patients in need, in line with national guidelines. **Most importantly, the availability of generic linezolid would help save DR-TB patients' lives.**

Clinicians across South Africa consistently struggle to offer adequate treatment regimens for patients with DR-TB. The current treatment course for DR-TB is at least two years, and patients sometimes take more than 20 pills per day and suffer painful injections for the first six months of treatment. The only medicines available can have devastating side effects—including deafness and psychosis—and the cost of a treatment regimen is significantly higher than that for standard, drug-sensitive TB.

World Health Organisation³ and national⁴ guidelines in South Africa recommend linezolid as a third-line drug for DR-TB treatment, when cost permits. These guidelines highlight the importance of linezolid in designing treatment regimens strong enough to combat extensively drug-resistant TB (XDR-TB) and pre-XDR TB. The drug is also one of few available options for patients who do not tolerate standard DR-TB therapies. We estimate that every year, at least 1,000 patients diagnosed with DR-TB in South Africa would be eligible candidates for a linezolid-containing regimen, if cost were not a prohibitive factor. For DR-TB patients, access to an adequate regimen means the difference between life and death.

Earlier this year, the sinister intentions of the multinational pharmaceutical industry to block access to generic medicines were made glaringly obvious. Documents leaked to the media revealed a US\$600,000 plot by 25 multinational pharmaceutical companies to protect profit margins at the expense of public health, by delaying reform of South Africa's patent laws through a covert campaign.⁵ In order to counter the corporate interests exposed during "Pharmagate," strong leadership that promotes access to medicines and advances the constitutional right to access healthcare services in South Africa is required from state bodies like the MCC. Registration of generic linezolid would be a clear step forward in the right direction, and help address a disease and public health emergency that is the leading cause of death in South Africa. Further delays in registering a quality-approved generic are unconscionable.

We urge the MCC to register generic Hetero linezolid as a matter of urgency, or to provide urgent clarification on why registration is being delayed. We look forward to your prompt response.

Sincerely,

Current and Former DR-TB Patients Who Have Benefitted from the Inclusion of Linezolid in their Treatment Regimens

Phumeza Tisile—Khayelitsha, Western Cape
Andaleeb Rinqest—Cape Town, Western Cape
Morgan Scholtz—Kleinkranz, Western Cape
Mary McNally—Cape Town, Western Cape

³ http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf?ua=1

⁴ <http://www.hst.org.za/sites/default/files/TBpolicy.pdf>

⁵ <http://keionline.org/node/1908>

Organisations:



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Accredited to the Hospice Palliative Care Association



(Doctors Without Borders South Africa)

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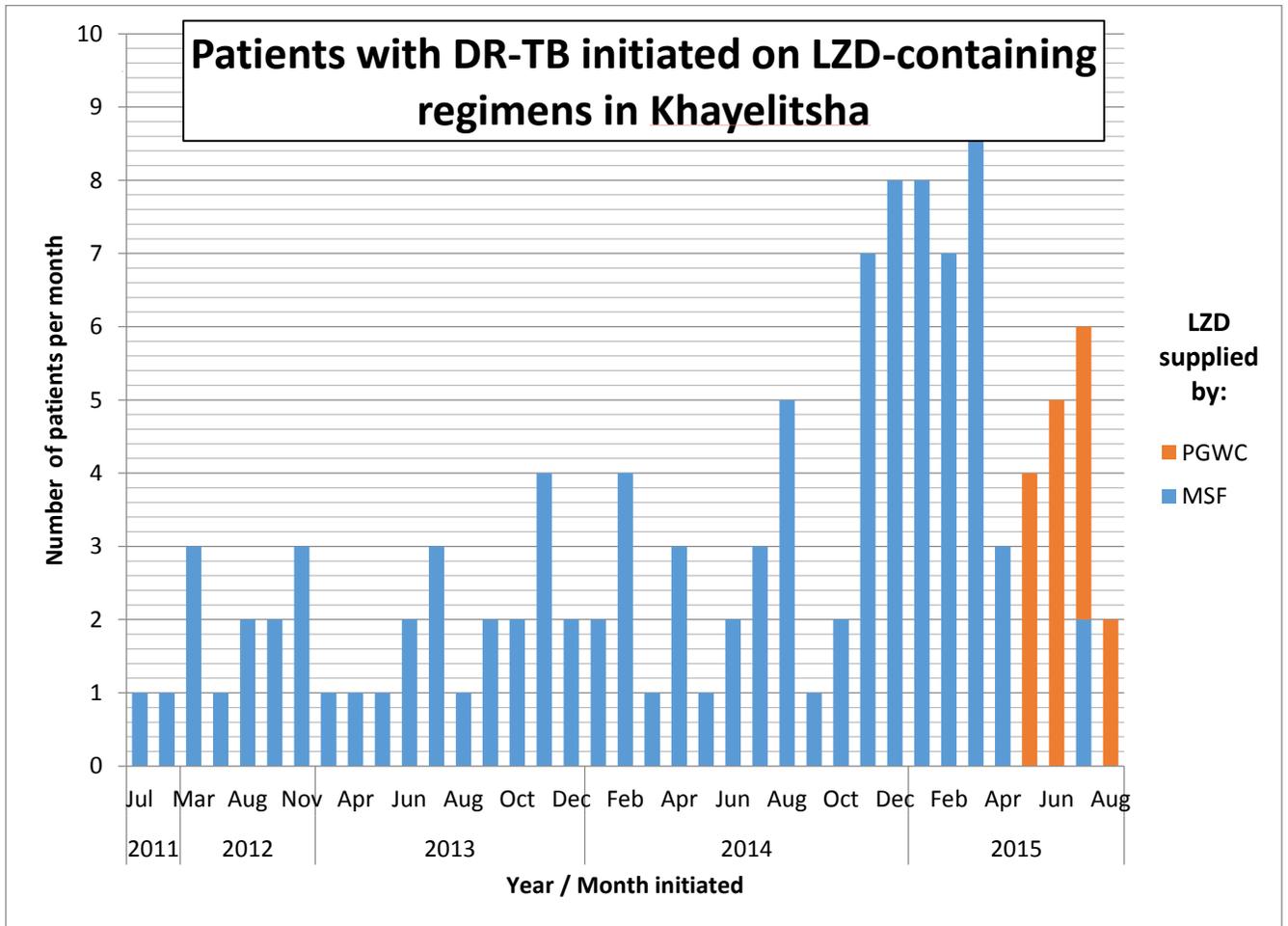
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Iain Watermeier

Annex 2:



Annex 3:

2015 Linezolid Prices in South Africa						
Supply Source	Private sector price/600mg tablet		Discount price/600mg tablet (<i>offered June 2015 to the Provincial Govt of Western Cape</i>)		Lowest approx. price per patient for 2-year linezolid supply (<i>1x600mg tablet daily</i>)	
	ZAR	USD	ZAR	USD	ZAR	USD
Pfizer	855	62	214*	15.50	162,640	11,293
Sanofi (<i>marketing Hetero</i>)	655	47	159*	11.50	116,070	8,394
MSF†	109	7.90	590 **	42.50	79,570	5,753
Global Drug Facility	N/A	N/A	74.7-76.5	5.35-5.48	54,537	3,906

^All currency conversions as of November 4, 2015 on <http://www.xe.com/currencyconverter/>

† Purchasing Hetero product via MSF supply channels unless otherwise noted. Only used in MSF project area in Khayelitsha, Western Cape.

*Offered June 2015 to the Provincial Government of the Western Cape.

**Quoted by Sanofi to MSF during 2015, for small batches needed to fill a supply gap, for provision to public sector patients in MSF project area of Khayelitsha, Western Cape.