

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, 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,

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