The 20th Expert Committee on the Selection and Use of Essential Medicines
Department of Essential Medicines and Health Products
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

30 January 2015

RE: Support for the addition of linezolid to the World Health Organization Model List of Essential Medicines

Dear Expert Committee,

There is an urgent need to expand access to linezolid, a drug in the oxazolidinone class used off-label to treat multidrug-resistant (MDR-) and extensively drug-resistant (XDR-) tuberculosis (TB). Drug-resistant forms of TB are increasingly common. Mounting evidence points to linezolid's effectiveness against TB in people with drug-resistant TB. Moreover, as new TB drugs bedaquiline and delamanid (also under consideration for addition to the Model List of Essential Medicines) emerge, companion drugs such as linezolid to protect against the development of resistance to these drugs are essential. And with several generic products available, linezolid's price is reducing.

Linezolid is a very important drug for people with MDR- or XDR-TB with few other options. A growing body of data on linezolid's effectiveness in treating MDR- and XDR-TB (including in children and in people with HIV) support its inclusion on the List. A meta-analysis of 12 nonrandomized studies of linezolid's role in MDR- and XDR-TB treatment found that 82 percent of patients treated with linezolid were cured or completed treatment—higher than in previously reported XDR-TB treatment outcomes.[1] A U.S. National Institute for Allergies and Infectious Diseases-sponsored small clinical trial in Korea found that linezolid successfully led to sputum culture-conversion in 87% of patients with XDR-TB within six months of treatment.[2] A recent clinical trial of linezolid in 65 participants with XDR-TB found that the treatment success rate in the linezolid therapy group was 69.7%, nearly twice as high as in the control group (34.4%; p=.004).[3] Long-term use of linezolid is associated with increased risk for some serious adverse events, including bone marrow suppression and neuropathy; however, these risks are far outweighed by the risk of inadequately treating drug-resistant TB, and potentially managed clinically through dose adjustments and schedules.[4] The *Companion handbook to the WHO guidelines for the*

programmatic management of drug-resistant tuberculosis lists linezolid as an option for some patients with MDR- and XDR-TB.[5]

Recent advances (resulting in part from advocacy efforts) have dramatically reduced the price of linezolid in a short period of time. (Access to linezolid for those with MDR- and XDR-TB in need has been hampered by high pricing of the originator drug, and its lack of an indication for TB.) For example, manufacturer Hetero developed a generic version of linezolid and received quality assurance and stringent regulatory authority approval for it; this generic linezolid is available via the Global Drug Facility for just US$6.9 per 600 mg pill, about one-tenth of the US$65 per pill price tag for Pfizer's originator linezolid (Zyvoxid) in South Africa. Several additional manufacturers are expected to soon receive approval for generic versions of linezolid, which will likely further reduce the cost of the drug.

The inclusion of linezolid on the EML will encourage greater access to this drug while providing national tuberculosis programs with clearer guidance on how to incorporate it into existing MDR- and XDR-TB treatment regimens.

We appreciate your consideration of this letter of support and urge you to add linezolid for the use of TB to the List. Should you have any questions or interest in further discussion, please feel free to contact erica.lessem@treatmentactiongroup.org.

Sincerely,

Community Research Advisors Group
Global TB Community Advisory Board
Treatment Action Group
TB Proof

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[1] Sotgiu G, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J. 2012;40(6):1430–1442. doi: 10.1183/09031936.00022912.

[2] Lee M, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. NEJM. 2012 Oct;367(16):1508–18. doi: 10.1056/NEJMoa1201964.

[3] Tang S, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. ERJ. 2015 Jan;45(1):161-70. doi: 10.1183/09031936.00035114.

[4] World Health Organization. *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*. Retrieved from http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf?ua=1&ua=1. (Accessed 2015 January 26).