



Rue de Lausanne 78
Case Postale 1016
1211 Geneva 1, Switzerland
Tel: +41 (0) 22 849 84 05
Fax: +41 (0) 22 849 84 04

OPEN LETTER TO J&J REGARDING AFFORDABLE ACCESS TO BEDAQUILINE

17 September 2018

Dr Paul Stoffels
Vice Chair of the Executive Committee and Chief Scientific Officer
Johnson & Johnson Global Public Health
1 Johnson & Johnson Plaza
New Brunswick, NJ 08933, USA

CC:

Jennifer Taubert, Executive Vice President, Worldwide Chairman, Pharmaceuticals
Ana-Maria Ionescu, Senior Director, Global Marketing Leader TB, Global Public Health
Dr Adrian Thomas, Vice President, Global Market Access, Global Commercial Strategy Operations
and Global Public Health

Re: Securing an affordable and sustainable supply of lifesaving TB drug bedaquiline

Dear Dr Stoffels,

For the past decade, Médecins Sans Frontières (MSF) has been in dialogue with Johnson & Johnson (J&J) about the critically important TB drug bedaquiline, including on access to bedaquiline for MSF-run clinical trials, compassionate use of bedaquiline for people with extensively drug-resistant TB (XDR-TB), and routine use of bedaquiline to treat multidrug-resistant TB (MDR-TB) in MSF medical projects. We are writing now to J&J regarding the need for all countries to secure an affordable and sustainable supply of bedaquiline given the expanded use of bedaquiline to treat more forms of MDR-TB globally.

Bedaquiline saves lives

In 2013, soon after its registration based on limited phase II safety and efficacy data, the World Health Organization (WHO) recommended the use of bedaquiline as an add-on agent in its MDR-TB treatment guidelines based on the consideration that new and improved treatments for MDR-TB were desperately needed because success rates using available treatments remained low.

On 17 August 2018, based on accumulated experience with bedaquiline in clinical practice, the WHO issued an update to its treatment guidance¹ expanding the use of bedaquiline by making it a core drug in standard regimens to treat MDR-TB. This effectively increases the number of patients for whom bedaquiline treatment is recommended and necessitates national TB programmes to scale up access to bedaquiline-containing regimens. Positive results from studies currently underway on the use of bedaquiline in all-oral, shorter-course regimens could result in an even greater potential patient benefit and wider use of bedaquiline in TB programmes globally. To date, only 25,000 people have received bedaquiline worldwide – nearly 70% of whom have been treated in South Africa.²

However, obtaining affordable access to bedaquiline for patients in high TB burden countries has until recently relied on either the J&J/USAID donation programme or bilateral price negotiations with J&J or its partners. The recent reduction to US\$400 for a six-month treatment course for some countries, including South Africa and those procuring through the Global Drug Facility (GDF), is noted. However, this price remains excessive for the countries hardest hit by MDR-TB.

A long-awaited new TB drug

Bedaquiline was granted accelerated approval by the US Food and Drug Administration (FDA) in 2012 as part of combination treatment in adults with pulmonary MDR-TB.³ Conditional marketing authorisation for bedaquiline was subsequently granted by the European Medicines Agency (EMA) in 2013. Both the US FDA and EMA provided approval based on limited safety and efficacy data from a phase IIb study to fulfil an unmet medical need as MDR-TB is a life-threatening disease which represents a health emergency of global proportions. In both cases, approval came with the requirement of conducting additional studies to confirm clinical benefit. When bedaquiline was authorised, it was the first new TB drug that was specifically developed for TB in nearly 50 years, thereby raising hopes for hundreds of thousands of people infected with forms of TB that had been practically untreatable.

The development of bedaquiline benefited from significant public funding and support

While J&J did not conduct phase III trials as part of their initial bedaquiline development programme, several of the phase I and II trials conducted prior to the drug's registration were sponsored by the US National Institutes of Health/National Institute of Allergy and Infectious Diseases^{4,5} and the TB Alliance.^{6,7} A phase III trial (STREAM II) including bedaquiline is currently underway, but it is sponsored by the International Union Against Tuberculosis and Lung Disease and funded by USAID.⁸ Together with Partners in Health and other partners, MSF is also sponsoring a phase III clinical trial including bedaquiline, with funding from UNITAID.⁹ Meanwhile, J&J earned a tropical disease priority review voucher (PRV) for bedaquiline, which the company used to accelerate review and marketing authorisation of guselkumab, a blockbuster psoriasis drug that sells for nearly US\$60,000 per patient per year in the US and is estimated to yield US\$3.49 billion in sales by 2024¹⁰. Pharmaceutical companies have sold tropical disease PRVs for as much as US\$350 million.¹¹ As bedaquiline was also granted orphan drug designation, J&J further benefitted from a 50% tax credit on qualifying clinical research and development expenditure as well as exclusive US marketing rights for seven years.

Building the evidence base for bedaquiline as a core MDR-TB drug was a collective effort

Indeed, following the approval of bedaquiline based on phase II data, several research institutes, treatment providers, including national TB programmes and MSF, have invested in additional trials, operational research, and pharmacovigilance to further document the safety, efficacy and optimal use of bedaquiline for the treatment of MDR-TB. These significant contributions are financed with public and philanthropic resources and conducted as a collective effort by a TB community desperate to provide people with MDR-TB with improved treatment options. The recent WHO recommendations of bedaquiline as a core drug for the treatment of MDR-TB are largely based on the data and experience produced through these collective efforts.

Affordable access should be prioritised and reflect the collective investment

The TB community and public funders have made an important collective investment in demonstrating the public health value of bedaquiline, including through ongoing trials that will enable long-awaited shorter-course, all-oral treatments that have the potential to transform our ability to tackle this deadly disease. Given the critical public health value of bedaquiline for the treatment of MDR-TB and given the financial windfall J&J has enjoyed as a result of its PRV, we believe J&J has a clear responsibility to do more to ensure affordable access to bedaquiline. While J&J holds proprietary patents covering bedaquiline in many countries, the public and philanthropic contributions made to date warrant a guarantee of public return on these investments as well as a common right to use that ensures bedaquiline is accessible to all MDR-TB patients who need it.

J&J can demonstrate its commitment to people living with TB worldwide by taking the following specific steps.

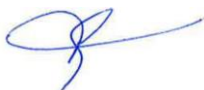
MSF urges J&J to:

- **Register bedaquiline:** Domestic registration is key for national TB programmes to incorporate bedaquiline as a core drug in MDR-TB regimens. MSF acknowledges the efforts J&J and its partner, Pharmstandard, have made in recent years to register bedaquiline in their respective geographical territories – the Commonwealth of Independent States and Georgia for Pharmstandard, and the rest of the world for J&J. However, there are 18 high-burden countries where bedaquiline is not yet registered. MSF urges J&J and its partners to expedite registration in these countries and make information on registration plans and registration status public. In addition, in countries where bedaquiline is already registered, J&J should promptly share available paediatric use data and start the process to request an extension of indication for children aged six years and above with all national regulatory authorities.
- **Lower the price of bedaquiline:** MSF and others have called for MDR-TB treatment regimens to be priced below \$500 per person. Researchers have concluded that bedaquiline can be manufactured and sold profitably for prices between \$8 and \$16 per month.¹² Accordingly, it is reasonable to expect that bedaquiline should be priced no higher than \$32 per month, which would play a major role in facilitating the rapid scale-up of new WHO-recommended regimens. Fair and transparent pricing should be available in all countries through J&J and its partners, including in low- and middle-income countries and high-burden countries. In this context, we would also like to draw your attention to the price that your commercial partner, Pharmstandard, charges in Commonwealth of Independent States countries. The price – US\$264 per month (US\$1,584 per six months) – is significantly higher than the price of US\$67 per month available to countries purchasing through the GDF.
- **Issue a non-exclusive license for bedaquiline:** In the past, dependence on a sole supplier for production of essential medicines has not only kept prices high, but has also led to shortages and sudden breaches in supply due to unforeseen circumstances.^{13,14} Because bedaquiline base compound patents will not begin to expire in different jurisdictions until 2023, generics manufacturers will not be able to supply the drug to TB programmes for more than five years from now – even if WHO-prequalified – unless a non-exclusive voluntary license is issued. In order to ensure sustainable supply through additional manufacturers, MSF urges J&J to issue a non-exclusive voluntary license to the Medicines Patent Pool. The geographic scope of the license should cover at least all low- and middle-income countries and all high TB burden countries in order to ensure long-term sustainable supply to TB programmes.
- **Stop further monopoly building around bedaquiline:** MSF urges J&J to refrain from patent evergreening strategies that will further delay the availability of quality-assured generic versions of bedaquiline. J&J applied for and received a patent on the salt form of bedaquiline in South Africa¹⁵ that extends its monopoly on the drug until 2027, creating unwarranted additional barriers for the supply of generic versions of the drug. We urge J&J to abandon or withdraw from such evergreening patents and provide full transparency on the patents it holds or is pursuing that may hamper the timely availability of generic versions of bedaquiline.
- **Provide access to bedaquiline for patients whose treatment must extend beyond six months:** For patients whose drug susceptibility testing (DST) diagnosis confirms extensive drug resistance and who have an insufficient number of effective drugs in the continuation phase, J&J should facilitate and ensure the availability of bedaquiline to treatment providers beyond six months, as interruption of bedaquiline could result in culture reversion, drug resistance and treatment failure. We would like to explore solutions for these patients with J&J's medical team.

Given the critical public health importance of bedaquiline and its *capacity to save lives*, as well as the fact that the development of the drug and demonstration of its clinical benefit have been driven in large part by public funds and the TB community, we believe bedaquiline should be recognised as the fruit of a collective effort. We call on J&J to demonstrate bold leadership in ensuring affordable access to bedaquiline for everyone who needs it to survive.

We look forward to receiving your responses to the requests above and we welcome the opportunity to discuss these issues with you further.

Sincerely,



Dr Els Torreele
Executive Director

¹ WHO. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis 2018. [Online]. 2018 [Cited 2018 Aug 25]. Available from: http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1.

² DR-TB STAT. Country Updates. [Online]. 2018 [Cited 2018 Aug 30]. Available from: <http://drtb-stat.org/country-updates/>

³ U.S. Department of Health and Human Services, Food and Drug Administration. Accelerated approval, SIRTURO (bedaquiline) 100 mg tablets. [Online]. 2012 [Cited 2018 Aug 25]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/apletter/2012/204384Orig1s000ltr.pdf

⁴ National Institute of Allergy and Infectious Diseases. A Phase I Open-Label Trial To Investigate the Pharmacokinetic Interaction Between Rifabutin Or Rifampin And A Single Dose Of TMC207 In Healthy Subjects. [Online]. 2017 Apr 21 [Cited 2018 Aug 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01341184>

⁵ National Institute of Allergy and Infectious Diseases. A Phase I, Safety, Tolerability, and Pharmacokinetic Interaction Study of Single-Dose TMC207 and Efavirenz in Healthy Volunteers. [Online]. 2013 Apr 4 [Cited 2018 Aug 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT00992069>

⁶ Global Alliance for TB Drug Development. A Phase II Trial to Evaluate the Early Bactericidal Activity, Safety and Tolerability of the Following: TMC207 Alone, TMC207 Plus Pyrazinamide, TMC207 Plus PA-824, PA-824 Plus Pyrazinamide and PA-824 Plus Pyrazinamide and Moxifloxacin, in Adult Patients With Newly Diagnosed, Smear-Positive Pulmonary Tuberculosis. [Online]. 2017 Feb 28 [Cited 2018 Aug 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01215851>

⁷ Global Alliance for TB Drug Development. A Phase II Dose Ranging Trial to Evaluate the Extended Early Bactericidal Activity, Safety, Tolerability, and Pharmacokinetics of TMC207 in Adult Patients With Newly Diagnosed, Uncomplicated, Smear-Positive, Pulmonary Tuberculosis. [Online]. 2017 Apr 26 [Cited 2018 Aug 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01215110>

⁸ IUATLD, Inc. STREAM: The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB. [Online]. 2018 Jan 26 [Cited 2018 Aug 30]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02409290>

⁹ MSF. Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB): A Clinical Trial. [Online]. 2018 Apr 12. [Cited 2018 Sep 4]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02754765>

¹⁰ EvaluatePharma. World Preview 2018, Outlook to 2024. [Online]. 2018 Jun [Cited 2018 Aug 25]. Available from: <http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf>

¹¹ Kerr KW, Henry TC and Miller KL. Is the priority review voucher program stimulating new drug development for tropical diseases? PLoS Negl Trop Dis. [Online]. 2018 Aug 9 [Cited 2018 Aug 30]. Available from: <https://doi.org/10.1371/journal.pntd.0006695>.

¹² Dzintars G, Fortunak J, Pozniak A et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. Journal of Antimicrobial Chemotherapy. [Online]. 2017 Jan 10 [Cited 2018 Aug 25]. Available from: <https://doi.org/10.1093/jac/dkw522>

¹³ Nurse-Findlay S, Taylor MM, Savage M et al. Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews. PLOS Medicine. [Online]. 2017 Dec 27 [Cited 2018 Aug 25]. Available from: <https://doi.org/10.1371/journal.pmed.1002473>

¹⁴ MSF. South Africa should override patent on key HIV medicine after widespread stock out problem. [Online]. 2015 October [Cited 2018 Aug 25]. Available from: <https://www.msf.org/south-africa-should-override-patent-key-hiv-medicine-after-widespread-stock-out-problem>

¹⁵ Medicines patents and licences database. South Africa: bedaquiline 100mg. [Online]. 2018 [Cited 2018 Aug 25]. [http://www.medsdal.org/?product_standardized_name=Bedaquiline 100 mg&country_name=South Africa](http://www.medsdal.org/?product_standardized_name=Bedaquiline+100+mg&country_name=South+Africa)