

TO: Akihiko Otsuka, Chairman
Taro Iwamoto, President
Masuhiro Yoshitake, Executive Operating Officer and TB Global Project Leader

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Open Letter: Urgent Appeal to Initiate Delamanid Compassionate Use Program

Dear Otsuka leadership team,

We congratulate you on the recommendation from the Committee for Medicinal Products for Human Use (CHMP) to the European Medicines Agency (EMA) to grant marketing approval to delamanid. New tools such as delamanid to treat multi-drug resistant tuberculosis (MDR-TB) are critically important to save lives. Otsuka's investments to date in TB research and development have been essential; we now urge you to ensure delamanid is accessible to patients who urgently need new treatment options.

Otsuka has been the leading corporate funder of TB research since 2006, according to Treatment Action Group's annual *Report on Tuberculosis Funding Trends*. Otsuka's timely initiation of its pediatric studies of delamanid, and efficient enrollment of a phase III trial, are models for the field. We also appreciate Otsuka's willingness to work with the U.S. National Institutes of Health (NIH) to allow for the study of delamanid and bedaquiline, the other new drug to fight MDR-TB, in combination. Yet, we are deeply concerned that Otsuka has failed to approach delamanid's access with similar responsible diligence.

Most pressingly, we are disturbed that delamanid has not yet become available under well-established pre-approval mechanisms, such as compassionate use programs and expanded access trials. The TB CAB has been pressing Otsuka to implement a pre-approval access program since November 2011, including in [an open letter in May 2012](#). Since then, a phase III trial has been enrolled, the drug is poised for stringent regulatory approval-- and yet, not a single patient has been able to access the drug outside of a safety or efficacy trial. This failure from Otsuka to provide responsible early access to its drug stands in sharp contrast with the successful expanded access program that is currently underway with bedaquiline, although bedaquiline is in an earlier clinical development stage than delamanid.

Pre-approval access mechanisms, delineated in various guidance documents such as the *Good Participatory Practice Guidelines for TB Drug Trials* and the EMA's *Guideline on Compassionate Use of Medicinal Products*, are designed to responsibly allow for controlled access to investigational new products when no satisfactory alternative therapy exists or when patients cannot enter a clinical trial. Patients with extensively drug-resistant TB (XDR-TB), pre-XDR-TB or an inability to tolerate drugs for MDR-TB are in urgent need of new treatment options such as delamanid. They cannot wait for drug approval and access in their countries, which would take years. Many of these patients live in communities participating in your phase III and phase II trials (which were the basis for a positive opinion from the CHMP) and yet cannot benefit from the investigational trial—this violates principles of ethical conduct of research, such as those stipulated in the World Medical Association's *Declaration of Helsinki*.

We therefore advise you to open enrollment of a compassionate use program by the end of 2013. This program may include, but must not be limited to, implementing partners such as Médecins Sans Frontières (MSF). We also urge Otsuka to price delamanid affordably once it receives approval, to rapidly register it in countries affected by TB, and to commit to further research to optimize the use of the drug (including confirming that the current dose of delamanid is the appropriate one, as recommended by the CHMP).

Your continued failure to comply with this request will signal a direct violation of Otsuka's stated corporate philosophy to "build harmonious relationships with local communities...while pursuing the goal of contributing to better health and more prosperous lives for people everywhere."

Thank you for your meaningful investments in TB research to date; we sincerely hope for your partnership moving forward.

We look forward to your favorable response,

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

CC: Patrizia Carlevaro, Managing Director, Otsuka SA