The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents

Interim policy guidance

THE END TB STRATEGY

World Health Organization

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Abbreviations

ART	antiretroviral therapy
AUC	area under the curve
BID	bis in die (Latin for “twice a day”)
BMI	body mass index
Cl/F	apparent oral clearance
Cmax	maximum plasma concentration
CU	compassionate use
DOI	declaration of interest
DST	drug-susceptibility testing
EBA	early bactericidal activity
ECG	electrocardiogram
EMA	European Medicines Agency
ERP	External Review Panel
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant tuberculosis
OBR	optimized background regimen
PD	pharmacodynamics
PICO	population, intervention, comparator, outcome
PK	pharmacokinetics
PMDT	programmatic management of drug-resistant tuberculosis
RCT	randomized controlled trial
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
US	United States
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Acknowledgements

This document was prepared by Christian Lienhardt and Lice González-Angulo with contributions from Dennis Falzon, Ernesto Jaramillo and Karin Weyer (WHO Global TB Programme), based on outputs of the Guideline Development Group (GDG) meeting that was convened by World Health Organization in Geneva, Switzerland on 28 - 29 June 2016.

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This document was finalized following consideration of all comments and suggestions made by members of the GDG and the External Review Panel.

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Declarations of interest

Declaration of interest forms were completed by all non-WHO members of the Guideline Development Group (GDG) and the External Review Group, and by the members of the academic centres who were involved in the reviews. One member of the GDG (Daniela Cirillo) declared interests that were judged to be non-significant, and five experts disclosed interests that were deemed to be significant, as outlined below:

- Grania Brigden indicated that her employer (Médecins Sans Frontières) received a donation of 400 treatments of delamanid (programmatic use) from Otsuka pharmaceuticals (manufacturer of delamanid) in February 2016. This was a one-off donation and is not expected to be repeated because MSF now procures delamanid directly from the Global Drug Facility.

- At the time of the guidance revision, Anneke Hesseling was the principal investigator in two Phase II, open-label, multiple-dose trials funded by Otsuka pharmaceuticals (Study 242-12-232 and Study 242-12-233). She has also received research support to fund a multisite Phase I/II trial of bedaquiline in HIV-infected and HIV-uninfected children with multidrug-resistant tuberculosis (MDR-TB), through the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network (P1108). Anneke Hesseling joined the meeting remotely via web conferencing.

- Erica Lessem disclosed that her employer (Treatment Action Campaign) received a total of $108 000 as means of general support from Janssen Pharmaceutical / Tibotec Therapeutics from 2010 to 2015. These funds were allocated to the Hepatitis C/HIV Programme and not to her work or the TB/HIV Project.

- Alena Skrahina contributed to the development of the document “Rapid clinical advice – the use of delamanid and bedaquiline for children with drug-resistant tuberculosis”, which was made publically available on 20 May 2016 via the TB Online portal. The document provides clinical statements related to the subject of the meeting.

- Fraser Wares’s employer, KNCV, manages the United States Agency for International Development (USAID)–Johnson & Johnson bedaquiline donation programme through its Challenge TB project.

In consultation with the WHO departments *Compliance, Risk Management and Ethics* and *Legal*, and the Chairman of the GDG meeting, the WHO Guideline Steering Committee at the Global TB Programme decided to assign these experts the status of “technical resource persons”, allowing them