The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

World Health Organization

This guidance was developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development on, 2012 available at http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf.

WHO Library Cataloguing-in-Publication Data

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance.

1.Bedaquiline. 2.Antitubercular agents – administration and dosage. 3.Tuberculosis, Multidrug-Resistant – drug therapy. 4.Treatment outcome. 5.Guideline. I.World Health Organization.

ISBN 978 92 4 150548 2 (NLM classification: WF 360)

Printed by the WHO Document Production Services, Geneva, Switzerland

WHO/HTM/TB/2013.6

Editing and design by Inís Communication – www.iniscommunication.com

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Supporting internet materials

- Expert Group Meeting report, including PICO question;
- *The contribution of bedaquiline to the treatment of MDR-TB – synthesis of publicly available evidence*, Bernard Fourie, South Africa;
- *Evaluation of sputum culture conversion as a surrogate marker of MDR-TB treatment outcome*, Ekaterina Kurbatova et al, CDC, Atlanta, GA, United States;
- *Cost-effectiveness of introducing bedaquiline in MDR-TB regimens – an exploratory analysis*, Anna Vassall, London School of Hygiene and Tropical Medicine, London, United Kingdom.

Available here:
http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html

Acknowledgements

This document was prepared by Christian Lienhardt, Karin Weyer, Dennis Falzon, Fraser Wares, Ernesto Jaramillo, Diana Weil and Mario Raviglione (World Health Organization (WHO), Stop TB Department) on the basis of consensus at an international Expert Group meeting convened by WHO in Geneva, Switzerland on 29–30 January 2013.

WHO gratefully acknowledges the contributions of the Chair of the Expert Group (Holger Schünemann), and its members (Elie Akl, Adekunle V. Babawele, Mauricio Baretto, Martien W. Borgdorff, Erlina Borhan, Richard E. Chaisson, Lucy Chesire, Erica Lessem, Norbert Ndjeka, Viet Nhung Nguyen, Joshua Obasanya, Michael L. Rich, Simon Schaaf, Francis Varaine, Andrew Vernon, Susanne van Den Hof and Piret Viiklepp) who jointly developed the recommendations, and the contributions from the technical resource consultants (Bernard Fourie, Ekaterina Kurbatova, Charles Peloquin and Anna Vassall).

WHO also acknowledges the contributions of the members of the External Review Panel (Jose A. Caminero, Gavin Churchyard, Anna Marie Celina Garfin, Giovanni Battista Migliori, Ashok Kumar, Helen McIlleron, Richard Menzies, Rohit Sarin, Alena Skrahina, Maarten van Cleeff). In addition, WHO acknowledges the specialized input from HIV experts Kelly Dooley, Diane Havlir and Gary Maartens, on concomitant use of bedaquiline and antiretroviral drugs.

This document was finalized following consideration of all comments and suggestions from the participants of the Expert Group and the External Review Panel. Technical editing was completed by Tim France, Inis Communication.

The United States Agency for International Development (USAID) is acknowledged for its support to the development of these guidelines through a USAID-WHO Consolidated Grant (project number: US 2012 0392). The US Centers for Disease Control and Prevention is acknowledged for its contributive work on the use of sputum culture conversion as a surrogate marker of multidrug-resistant tuberculosis (MDR-TB) treatment outcome (carried out by Ekaterina Kurbatova and colleagues).

Declarations of interest

All Expert Group (EG) members, technical resource consultants and members of the External Review Panel completed Declaration of Interest (DOI) forms. These were reviewed by the WHO Legal Department prior to the EG meeting and preparation of the current *Interim Policy Guidance*.

Two EG members (Erica Lessem and Andrew Vernon) declared receiving support from pharmaceutical companies for work not related to the present guidance. These declarations were deemed to be insignificant. The other members of the EG, as well as the technical resource consultants and the members of the External Review Panel, declared no interest.

Executive summary

Background

The emergence of drug resistance is a major threat to global tuberculosis (TB) care and control. The World Health Organization (WHO) estimates that up to half a million new cases of multidrug-resistant tuberculosis (MDR-TB) cases (i.e. resistant to, at least, rifampicin and isoniazid) occur each year globally. Current treatment regimens for MDR-TB are far from satisfactory: the overall duration is 20 months or more, requiring daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB, and have a high cost. Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully, largely as a result of a high frequency of patient deaths (15%) and loss to follow-up (28%), which is commonly associated with adverse drug reactions, among other factors. In a subset of 200 extensively drug-resistant tuberculosis (XDR-TB) patients in 14 countries, treatment success reached only 33% overall and 26% of the patients died. New drugs that would help build a better, safer, less toxic, shorter and cheaper regimen are therefore urgently needed to reduce patient suffering and mortality.

The landscape of TB drug development has evolved dramatically over the past ten years, and novel drugs are entering Phase III trials for the treatment of MDR-TB. Among these, a new drug, bedaquiline, has recently (December 2012) been granted accelerated approval by the United States Food and Drug Administration (US-FDA) based on Phase IIb data. Similar submissions are currently being made to other national regulatory authorities worldwide. WHO Member States have requested the organization to provide interim policy guidance on the use of bedaquiline as part of the treatment of MDR-TB.

It is acknowledged that developing interim guidance on the use of a new TB drug on the basis of Phase IIb trial data is a novel step for WHO. Issuing interim guidance carries with it the responsibility of ensuring that it provides specific recommendations on the conditions for the use of the drug that reflect the limited data currently available. It will also be necessary for WHO to review, revise and/or update the interim guidance as additional substantive data on efficacy and safety become available. Acceleration of Phase III trials and completion at the earliest opportunity is imperative, as is timely analysis of emerging operational data on the use of the drug. It should also be noted that, in the absence of interim guidance from WHO, uncontrolled and potentially irresponsible use of the drug may adversely affect TB care and control efforts overall – potentially prompting the emergence of bedaquiline resistance and the possible loss of the first new TB chemotherapeutic drug in over 40 years.

Objectives, rationale and methods used to develop the guidance

This document provides interim guidance for the use of bedaquiline in conjunction with other WHO-recommended MDR-TB treatments. It also specifies the essential treatment and management conditions for the use of this drug. The main audiences are national TB control programmes (NTP), other public health agencies, and other public and private partners involved in planning, implementing and monitoring MDR-TB control activities. The principles and recommendations are also relevant for specialist clinicians, technical advisors, laboratory technicians, drug procurement managers, other service providers, other relevant government officials, and implementing partners involved in country-level MDR-TB service strengthening. Individuals responsible for programme planning, budgeting, resource mobilization, and training activities for MDR-TB diagnostic services may also benefit from this guidance.

An Expert Group (EG) was convened by the WHO/Stop TB Department in Geneva, Switzerland from 29th to 30th January 2013 to assess all available data on bedaquiline, and with a view to issuing interim policy recommendations on its use, as appropriate. Since efficacy and safety data available for this drug, used for the treatment of MDR-TB, are results from Phase IIb studies only (i.e. not Phase III trials), the potential guidance could only be provisional, until further clinical trial and safety data are available.

The overall objective of the EG meeting was to evaluate the added benefit of bedaquiline for the treatment of MDR-TB and, if appropriate, to provide recommendations to WHO for interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment.

The specific objectives were:

(1) To evaluate the efficacy and safety of bedaquiline in addition to currently WHO-recommended MDR-TB treatments.

(2) To evaluate the balance between harms and benefits of the drug, its potential cost-effectiveness, patient and provider preferences and concerns, and the feasibility of introducing the drug into MDR-TB programmes.

(3) To provide, as appropriate, recommendations on the use of the drug as part of