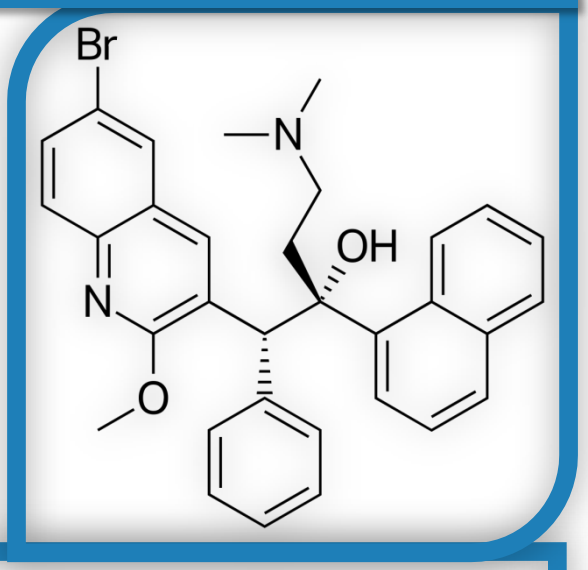
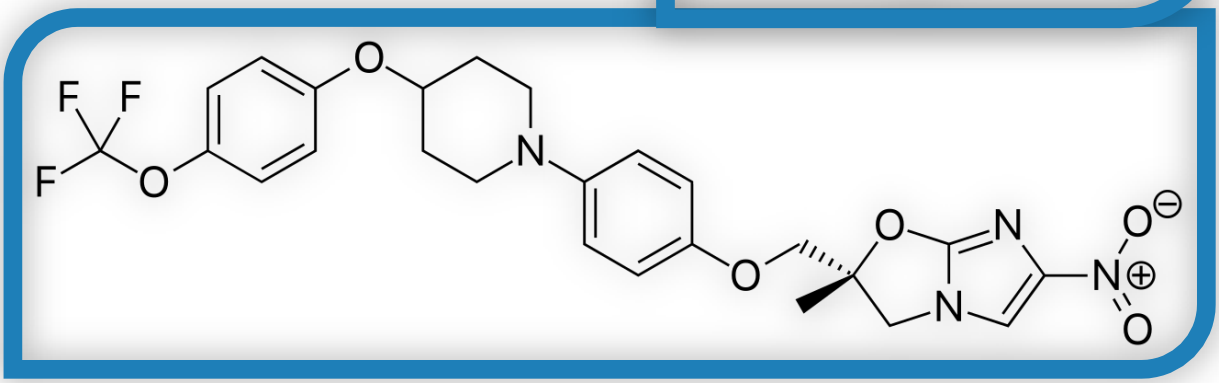
WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis





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WHO/HTM/TB/2017.20

Bedaquiline and delamanid – a brief timeline on registration and approval

Bedaquiline

- In December 2012, the United States Food and Drug Administration (US-FDA) approved bedaquiline, a new antibiotic, as part of combination therapy to treat adults with multidrug-resistant tuberculosis (MDR-TB) when other alternatives are not available(1),(2).
- The European Medicine Agency (EMA)(3) and other regulatory authorities approved bedaquiline in the following years, under very similar conditions as the US-FDA.
- WHO issued interim policy recommendations on the use of bedaquiline in June 2013(4); Provisional guidelines from the US Centers for Disease Control and Prevention followed later in the same year(5).
- In 2016, a WHO Guideline Development Group (GDG) reviewed new data from 537 MDR-TB patients treated with bedaquiline in observational studies in Armenia, France, Georgia, and South Africa, as well as data from a multi-site study conducted by the drug manufacturer, Janssen Pharmaceuticals, in 11 countries(6)[i].
- Based on the 2016 GRADE evidence assessment the GDG proposed no change to the overall interim WHO policy guidance on bedaquiline use. (i.e. the overall recommendation remained conditional[ii]). The specific condition for informed consent was aligned to the one made for delamanid in 2014(7), while the other four conditions governing use of both medicines remained unchanged, i.e. criteria for patient selection; compliance with the principles for the design of MDR-TB regimens; close patient monitoring and active drug-safety monitoring and management.

Delamanid

- In 2014, the EMA issued conditional approval for delamanid, a new antibiotic, as part of combination therapy to treat adults with MDR-TB when other alternatives are not available(8).
- WHO issued interim policy recommendations on the use of delamanid in 2014. These were updated in 2016 on the basis of new pharmacokinetic and pharmacodynamics (PK/PD) data to expand its use in children aged 6-17 years(7),(9).

Definitions and principles

- "Off-label use" is broadly defined as the use of a pharmaceutical agent for an unapproved indication or in an unapproved age group, different dosage, duration or route of administration(10)(Figure 1). In the absence of high-quality evidence, "off-label use" may be justified when:
  - the target condition is serious and there is other evidence to support potential benefit (particularly if the expected benefits outweigh potential risk);

[i] See meeting report at http://apps.who.int/iris/bitstream/10665/254712/1/WHO-HTM-TB-2017.01-eng.pdf

[ii] "Conditional" means that the recommendation can be adopted as policy in most situations(12). A conditional recommendation generally includes a description of the conditions under which the end-user should implement (or not implement) the recommendation. The interim WHO policy guidance for bedaquiline and delamanid therefore means that these medicines should be implemented by national TB programmes, under the conditions outlined in the interim policy guidance.

  - standard therapy is judged to be inadequate to achieve the desired outcome;
  - patients have been duly informed about the potential benefits and risks of "off-label use" and have consented (consent in writing may be necessary in some settings);
  - active and adequate monitoring of medicine safety is in place, including mechanisms to rapidly identify and manage adverse events.

- "Off-label use" is legal unless it violates ethical guidelines or safety regulations, which may vary between countries(11). The practice occurs in many specialties of medicine and is more likely in populations that are not well represented in clinical trials, such as children and pregnant women.
- Off-label use" falls under the purview of national regulatory agencies (i.e. a country-specific activity and responsibility). "Off-label use" is often applied by clinicians in the interest of individual patient benefit and requires proper coordination with national health services to ensure that it is in line with local regulations.
- Marketing of pharmaceuticals beyond their authorized indication is usually prohibited by regulatory authorities because of potential health risks and legal liability.
- For public health policy development, WHO is in principle against the use of medicines without appropriate supporting evidence ("off-evidence use", in distinction to "off-label use"). Adequate scientific data constitute the premise for WHO public health policy recommendations, under oversight of the WHO Guideline Review Committee (GRC)(12); http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf) and using the GRADE system for a rigorous, systematic, evidence-based approach to policy development(13).
- Current WHO treatment policies on bedaquiline and delamanid are interim given that the evidence for their use was based on safety and efficacy data from phase IIb clinical trials only(4),(7),(9). The policies will be reviewed and updated as additional data become available.
- In 2016, WHO updated its guidelines for the treatment of drug-resistant TB, including the classification of the medicines used in the design of longer treatment regimens for MDR-TB(14). These guidelines reiterated the role of bedaquiline and delamanid in strengthening longer MDR-TB regimens (for eligible patients) and also highlighted the important position of these two medicines in patients in whom the standardised shorter MDR-TB regimen cannot be used (including MDR-TB cases with additional resistance).
- Consolidated treatment guidelines for drug-resistant TB (including the interim policy guidance on bedaquiline and delamanid) will be produced by WHO later in 2017.

This document provides a best-practice statement on the "off-label use" of bedaquiline and delamanid in the treatment of MDR-TB (including those patients with additional drug resistance). This statement should not be interpreted as WHO recommending routine or broad off-label use of bedaquiline or delamanid; rather, the aim of the document is to support countries and clinicians in their own decisions on off-label use of these two products in individual patients. The document complements the most recent 2016 WHO treatment guidelines for drug-resistant TB(14)[iii] and will be integrated in the 2017 consolidated WHO treatment guidelines for drug-resistant TB as well as the accompanying WHO Companion Handbook to the WHO guidelines(15).

[iii] http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf

Drug-resistant TB treatment dilemmas and "off-label" use of medicines

- Treatment of drug-resistant-TB (DR-TB) - particularly rifampicin-resistant, multidrug-resistant or extensively drug-resistant forms - presents a number of challenges to clinicians and national TB programmes(14).
- The limited range of medicines available for treatment of drug-resistant TB and the frequent life-threatening nature of the disease often require "off-label use" of medicines, mainly in two situations[iv]:
  - The "repurposing" of a medicine registered for a condition other than TB. Thus, fluoroquinolones, kanamycin, amikacin, clofazimine, linezolid, carbapenems and clavulanic acid have been repurposed for use in drug-resistant TB treatment;
  - The use of a registered TB medicine in an unapproved age group, dosage, duration or route of administration than those indicated by its manufacturer and authorized by a stringent drug regulatory authority.
- Current WHO policy guidance for treatment of drug-resistant TB includes the use of medicines which have been registered for TB (including selected first-line TB drugs) as well as those repurposed for use in drug-resistant TB regimens(4),(7),(9),(14)[v].
- Evidence for the effectiveness and safety of repurposed medicines has grown and improved in recent years, although it remains heavily reliant on observational data(16),(17),(18). Knowledge about the safety of bedaquiline and delamanid remains incomplete due to the lack of adequate data.
- Given the life-saving potential of bedaquiline, delamanid and the repurposed medicines[vi] used in MDR-TB regimens, they are included in the WHO Model List of Essential Medicines(19),(20)

In the course of more widespread use of bedaquiline and delamanid in recent years, clinicians and national TB programmes have been challenged with situations in which they have few options other than to use these medicines outside of their registered indications in order to offer potentially life-saving treatment to patients with MDR-TB (including those with additional drug resistance). Examples of some common dilemmas and best-practice approaches are summarised below:

Situations which may prompt "off-label use" of bedaquiline or delamanid

- **Children and pregnant women:** due to a lack of evidence on safety and efficacy, bedaquiline is not recommended for use in children and pregnant women. Similarly, delamanid is not recommended during pregnancy or in children younger than 6 years. Use of delamanid in older children (6-17 years) has been recommended by WHO based on available PK/PD data.
- **Extrapulmonary tuberculosis:** both bedaquiline and delamanid were registered for use in pulmonary TB only. WHO policy guidelines accommodate their use in extrapulmonary forms of disease based on extrapolation of results from pulmonary TB; however, efficacy of both medicines remains unclear in extra-pulmonary TB, especially in serious forms such as meningitis.
- **Limited regimen options**: the basic principles of using five or more effective medicines in a longer MDR-TB regimen and not adding a single new agent to a failing regimen remain. However, some

[iv] These situations may co-exist, e.g. when fluoroquinolones are used in "high-dose" or for many months
[v] http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/en/
[vi] With the exception of gatifloxacin, which is not currently available on the market

patients may have extensive patterns of resistance or experience drug intolerance or serious adverse effects. Regimens of last resort in such patients may thus have to contain fewer effective medicines and should be used under prevailing ethical standards(11),(22).

- **Need for prolonged treatment duration:** both bedaquiline and delamanid have been registered to be used for a duration of 24 weeks(2),(8). Data on the safety and the added value of continuing bedaquiline or delamanid beyond the initial 24 weeks remain very limited(21). Nevertheless, clinicians and national TB programmes may be compelled to use these medicines beyond 24 weeks in selected MDR-TB patients (including those with additional drug-resistance) if the regimen is unlikely to achieve cure or poses a risk creating additional drug resistance.
- **Need for concomitant use:** data on the simultaneous use of the two medicines in the same patient are limited to individual case reports, e.g. (23), while findings from ongoing studies have yet to be published. No evidence-based WHO policy guidance is therefore currently possible[vii]. Concomitant use is not regarded as 'off-label use' and should be reserved for regimens of last resort in patients with extensive patterns of drug resistance, drug intolerance or serious adverse effects. Such regimens should be used under prevailing ethical standards(11),(22).

Best-practice approaches to "off-label use" of bedaquiline and delamanid

- Before resorting to "off-label use" of bedaquiline or delamanid, all reasonable measures should be taken to exhaust other valid therapeutic options. If a regimen is failing, it may need to be reviewed completely to ensure that its components are optimized and can overcome the emergence of further drug-resistance.
- For instance, it is important that the patient is taking all medicines in the regimen; that the quality of companion medicines is guaranteed (including expiry dates and conditions of storage); that dosages are optimised to avoid sub-therapeutic levels; and that interactions which may reduce the effectiveness of any of the medicines in the regimen are avoided.
- Decisions about "off-label use" of bedaquiline or delamanid should be taken on a case-by-case basis. Consultation with experts in management of MDR-TB should be sought (e.g. national MDR-TB committees or MDR-TB *consilia*).
- Patients need to be fully informed of the implications and provide informed consent (in accordance with local standards) to the "off-label use" of bedaquiline or delamanid. Parents or legal guardians may act for a child or for patients who are not capable of assenting. Prevailing ethical guidance should be followed(22).
- Close patient monitoring for response to treatment and active drug safety monitoring and management (aDSM) are mandatory, also for "off-label use" of bedaquiline or delamanid(24). Detailed data should be collected about each treatment experience as this may be very useful to inform both local and global policies.

[vii] The main concern is the additive effect that the two medicines can have on cardiac function, given that both agents are associated with a prolongation of the QT interval. Other, as yet unknown, drug-drug interactions also cannot be excluded.

Figure 1. "Off-label use" at-a-glance

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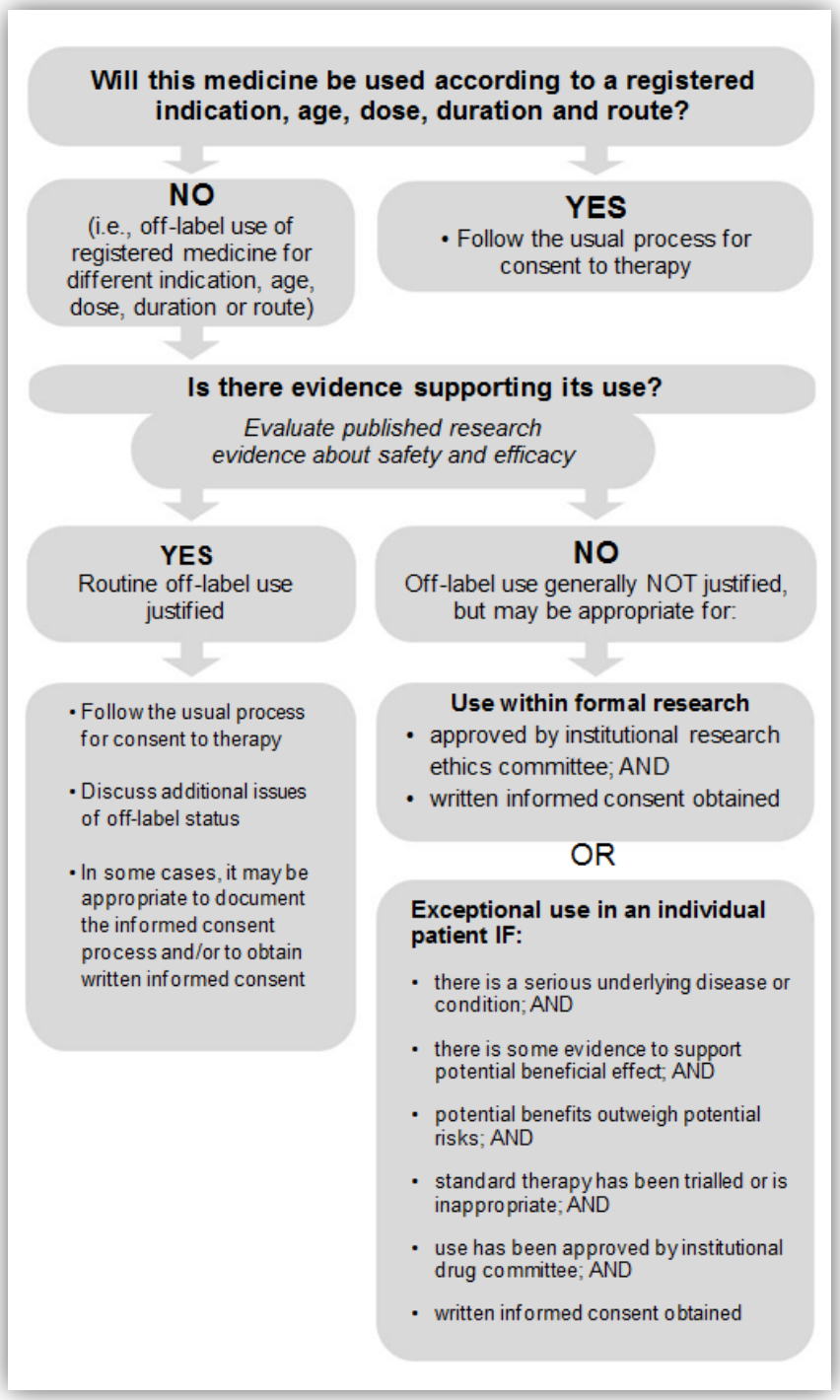

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