NHS England

Clinical Commissioning Policy: Bedaquiline and Delamanid for defined patients with MDR-TB and XDR-TB

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Document Status

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1 Executive summary

Policy Statement

NHS England will commission bedaquiline and delamanid for the treatment of proven multi-drug resistant and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB) in adults, in accordance with the criteria outlined in this document, and where there is documented evidence of resistance to fluoroquinolones or intolerance to second line drugs.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of these treatments for the population in England.

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Multidrug-resistant tuberculosis (MDR-TB) is when the TB bacteria fails to respond to a combination of 2 of the 4 main antibiotics used to treat the infection (first line anti-TB drugs), rifampicin and isoniazid. Patients usually acquire drug resistant disease either as a result of spread of a drug resistant strain from another person or as a result of inappropriate or incomplete treatment. Extensively drug-resistant tuberculosis (XDR-TB) is a form of TB that is resistant to at least four of the core anti-TB drugs (rifampicin, isoniazid, fluoroquinolones and second-line injectable agents).

Most patients with TB can be successfully treated with anti-TB drugs for a period of six months. The treatment of MDR-TB is difficult, expensive, and long, requiring administration of large numbers of drugs, many of which are only partially effective and most are toxic. Treatment is for periods of 20 months or more. Outcomes are poor, with successful treatment completion rates of less than 50%, approximately 15% mortality and as much as 28% of patients lost to follow up. The more extensively drug resistant variant of TB (XDR-TB) results in even worse outcome and mortality figures.

Bedaquiline has shown to be effective in reducing time to culture conversion in adult patients with pulmonary MDR-TB. Likewise delamanid has been shown to be effective in increasing the proportion of patients achieving sputum culture conversion after 8 weeks of treatment.

2 Introduction

Tuberculosis (TB) is an infectious disease that continues to represent a significant public health problem in England and worldwide. England has one of the highest incidence rates of TB within Western European countries (Public Health England, 2014). There is great variation in distribution of TB in England with certain sub-groups, such as new migrants, ethnic minority groups, and those with social risk factors disproportionally affected.

Drug resistance represents a major threat to TB control. Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis that is resistant to at least two anti-TB drugs, rifampicin and isoniazid. Extensively drug-resistant tuberculosis (XDR-TB)

is a form of TB that is MDR TB with additional resistance to any fluoroquinolone and to at least one of three injectable anti-TB drugs (i.e. kanamycin, capreomycin, or amikacin), and associated with high mortality, particularly among people living with human immunodeficiency virus (PLHIV).

The World Health Organization (WHO) estimates that up to half a million new cases of MDR-TB occur each year globally (WHO, 2013). The overall duration of current MDR-TB treatment regimens is 20 months or more, requiring daily administration of drugs that are more toxic, more expensive and less effective than those used to treat drug-susceptible TB. Only 48% of MDR-TB patients started on treatment globally in 2009, were treated successfully; a high proportion of these patients either died (15%) or were lost to follow-up (28%), often associated with adverse drug reactions, among other factors (WHO, 2013).

Treatment outcomes for patients with XDR-TB are even poorer; of a cohort of 200 patients with XDR-TB treated in 14 countries, the treatment success rate was only 33%, with high mortality (26%) (WHO, 2013). New drugs that would help develop better, safer, less toxic, shorter and cheaper treatment regimens are needed to reduce morbidity and mortality.

3 Definitions

- **TB**: Drug-susceptible TB; TB due to infection with a strain of *M. tuberculosis* that is susceptible to both isoniazid and rifampicin, although it might be resistant to other anti-TB drugs (mainly streptomycin).
- **MDR-TB:** Multi-drug resistant TB; TB due to infection with a strain of *M. tuberculosis* that is resistant to both isoniazid and rifampicin, the 2 most important first-line drugs to treat TB.
- **XDR-TB:** Extensively-drug resistant TB; infection with MDR strains of *M. tuberculosis* that are resistant to at least one of the second-line injectable drugs (amikacin, kanamycin, capreomycin) and any fluoroquinolone.
- **Bedaquiline:** A novel oral diarylquinoline anti-mycobacterial agent with a unique mechanism of action: the specific and selective inhibition of

mycobacterial ATP synthase, essential for energy generation in *M. tuberculosis*.

- **Delamanid:** A novel oral nitroimidazole anti-mycobacterial agent with a unique mechanism of action: the specific and selective inhibition of mycolic acid biosynthesis, essential for cell wall formation in *M. tuberculosis*.

4 Aim and objectives

This policy aims to:

- Define criteria for the commissioning of the use of bedaquiline and delamanid as an additional therapy in patients with MDR-TB and XDR-TB, with documented evidence of resistance to fluoroquinolones and/or intolerance to second line drugs.

The objectives are to:

- Improve treatment outcomes for patients with MDR-TB and XDR-TB.
- Reduce MDR-TB and XDR-TB transmission by achieving early culture conversion.

5 Epidemiology and needs assessment

The incidence of TB in England remains high compared to most other Western European countries. In 2013, there were 7,892 reported cases of TB in the UK, an incidence of 12.3 per 100,000 population (Public Health England, 2014). The majority of cases occurred in England (7,290) and of those, London accounted for the highest proportion (2,985 cases, 41%) followed by the West Midlands (981 cases, 13.4%).

Approximately 60% of cases were culture confirmed (4,680) and 98.4% of these had drug sensitivity testing to at least isoniazid and rifampicin (4,606). The proportion of TB cases with resistance to at least one first line drug (7.8 %) was similar to 2012 and slightly lower than in 2011, while the proportion of MDR-TB cases (1.6 % of culture confirmed cases) remained stable (74 cases). The majority of MDR-TB cases (87.3%) were born outside the UK. Although the total number of TB cases born in Eastern Europe remained low, a particularly high proportion of those that were culture confirmed had MDR-TB. Three cases of XDR-TB were reported in 2013. The proportion of MDR-TB cases who completed treatment by 24 months was 48%, with 22.5% still receiving treatment, 19.4% lost to follow up and 4 deaths (4.1%).

Cases of MDR-TB in the UK have increased over the last 12 years from 28 cases in 2000 to 89 cases in 2012. The total number of patients diagnosed with MDR-TB in the UK between 2000 and 2012 is 681. Considering the global epidemiology of MDR-TB and XDR-TB and the current patterns of migration, the number of cases is likely to increase in England. MDR-TB and XDR-TB are difficult to treat; treatment regimens are lengthy and often involve complex and expensive drugs with various side effects. Treatment requires considerable expertise, resources and integration of clinical, public health and social services, in order to improve treatment outcomes and reduce onward transmission.

6 Evidence base

Evidence base for Bedaquiline

Bedaquiline, first described in 2004 (Protopopova et al, 2007), is a novel diarylquinoline agent that specifically affects the proton pump of the *M tuberculosis* ATP synthase. The specific and selective inhibition of mycobacterial ATP synthase, essential for energy generation, makes bedaquiline a "first in class" drug with a distinct and novel target, not predicted to be associated with resistance to any other class of currently available drugs other than perhaps clofazimine (Hartkoorn et al, 2014). Mycobacterial resistance to bedaquiline may develop relating in part, but not entirely to, modification of the atpE target gene. Not all isolates with increased MICs have atpE mutations.

There is limited evidence assessing the efficacy and safety of bedaquiline for the treatment of MDR-TB and XDR-TB. Bedaquiline was granted accelerated approval by the United States Food and Drug Administration (US-FDA) in December 2012 (CDC, MMWR October 2013), based on evidence from two phase IIb trials (i.e., well-controlled trials to evaluate the efficacy and safety of drugs in patients with a disease or condition to be treated, diagnosed, or prevented), exclusively to be used for the treatment of adults with pulmonary MDR-TB and XDR-TB.

Bedaquiline's pharmacokinetic characteristics, drug-drug interaction (DDI) potential, and short-term safety and tolerability in healthy subjects and in a special population of moderately hepatic-impaired subjects were derived from 11 Phase I trials involving

265 subjects. Bedaquiline demonstrated good oral absorption, it is metabolised mainly by cytochrome P450 3A4 and has a prolonged half life. Eight single-dose trials involving 208 subjects receiving doses up to 800 mg bedaquiline; three multiple-dose trials involving 57 subjects receiving bedaquiline doses up to 400 mg daily for a maximum of 15 days. A double-blind, single-dose trial was conducted to evaluate the effect of a single supra-therapeutic (800 mg) dose of bedaquiline on the QT corrected (QTc) interval (WHO, 2013). A Phase IIa, 7-day extended early bactericidal activity trial in 75 patients with drug-susceptible TB (evaluating doses up to 400 mg bedaquiline daily) was conducted to evaluate clinical antimycobacterial activity (WHO, 2013).

The first published trial involving 47 patients with MDR-pulmonary TB randomly selected to receive either bedaquiline (23 patients) or placebo (24 patients) for eight weeks, in addition to WHO standard MDR-TB regime (Diacon et al, 2009) showed that the addition of bedaquiline reduced the time to culture conversion, as compared with placebo [HR=11.8 (95% CI:2.3, 61.3), p=0.003 by Cox regression analysis] and increased the proportion of patients with conversion of sputum culture (48% vs. 9%) (Hartkoorn et al, 2014).

Two phase IIb clinical trials (C208 and C209) have provided further evidence. Evidence for primary efficacy derives from the modified intention-to-treat (mITT) C208 two stages trial, of which Stage 1 was an exploratory study and Stage 2 was a multi-centre (15 sites in 8 countries), stratified, randomised, double-blind placebo-controlled trial, designed as a pivotal proof-of-efficacy study. Study C209 is a single-arm, open label trial that it is still ongoing.

The C208 trial involved 160 adults (18 to 65 years) with newly diagnosed pulmonary MDR-TB randomised to receive either oral bedaquiline (79 subjects, 400mg daily for 2 weeks followed by 200mg three times a week for the following 22 weeks), or placebo (81 subjects), in addition to a 5-drug MDR-TB regimen tailored to individual isolates. After week 24, all subjects continue to receive the 5-drug MDR-TB regimen for a further 96 weeks, total duration of study 120 weeks (Diacon et al, 2014).

The primary efficacy end point was time to sputum culture conversion (Commercial liquid culture MGIT^{TM} 960 Mycobacterial detection system, Becton Dickinson Diagnostic systems, USA). After applying exclusion criteria, 132 individuals (66 in each arm) were included. Median time to culture conversion was faster in the bedaquiline [83 days (95%CI: 56, 97)] than in the placebo arm [125 days (98, 168)]; HR=2.44 [(95%CI:1.57, 3.80), p<0.0001].

The secondary efficacy end point was proportion of patients with culture conversion at week 24; 78.8% of subjects in the bedaquiline arm *vs.* 57.6% in the placebo arm culture converted at week 24 (p=0.008). Culture conversion was also assessed at 72 and 120 weeks; the proportion of responders at 72 weeks was 71.2% *vs.* 56.1% in the bedaquiline and placebo arms respectively (p=0.069).

Utilising all available efficacy data up to end of study (week 120), 62.1% of patients in the bedaquiline arm culture converted *vs*. 43.9% in the placebo arm (p=0.035). The proportion of subjects defined as cured (WHO criteria) at 120 weeks was 58% in the bedaquiline *vs.* 32% in the placebo arm (p=0.003) (Diacon et al, 2014).

Bedaquiline was granted accelerated approval by the United States Food and Drug Administration (US-FDA) in December 2012, based on Phase IIb data. The FDA approval criterion was based on a surrogate outcome - the capacity of the drug, compared with placebo, to convert a patient's sputum culture from positive to negative for *M. tuberculosis* when added to a standard MDR-TB regimen- instead of mortality rates has been controversial (Avon, 2013).

Adverse events (AEs) were assessed using pooled data from Stages 1 and 2 (102 patients receiving bedaquiline and 105 subjects receiving placebo). Similar numbers of AEs were observed in both arms (>20%); the most commonly reported AEs in the bedaquiline arm were nausea, arthralgia, headache and vomiting. Additional AEs were dizziness, increased transaminases, myalgia, diarrhoea and QT prolongation on ECG.

Main safety concerns included QT prolongation, cardiac events, and deaths; there were 5 times more deaths in the bedaquiline arm than in the placebo group [10/79 (12.7%) vs. 2/81 (2.5%), p=0.017 (intention to treat analysis)].

Five of the 10 deaths in the bedaquiline arm were due to TB, indicating treatment failure as were the two deaths in the control arm. Further analysis of the deaths revealed no association with any co-morbidities or any other trial measure. Several of the remaining deaths in the bedaquiline arm could have been associated with hepatotoxicity as bedaquiline, in multiple dosing, can prolong the QT interval. This risk is highest during the treatment phase, but could extend beyond the treatment period (WHO, 2013).

In January 2013, the World Health Organisation (WHO) convened an expert group to evaluate existing evidence for the use of bedaquiline in addition to existing WHO recommended regimens for the treatment of MDR-TB, and to produce specific recommendations on the conditions for use, reflecting the limited available data on effectiveness and safety (WHO, 2013). The expert group produced conditional recommendations (low confidence of estimates of effect-low quality of evidence) that bedaquiline may be added to a WHO-recommended regimen in adult patients with MDR-TB when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed and when there is documented evidence of resistance to any fluoroquinolones in addition to MDR-TB (WHO, 2013).

In March 2014, the European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), granted approval for the use of bedaquiline in the European Union (including the UK) as part of an appropriate combination regimen for pulmonary MDR-TB in adults when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Critical evaluation of bedaquiline

The level of evidence for bedaquiline's efficacy and safety remains very limited to date. The safety of bedaquiline was reported to be similar to placebo groups and also across the various dosing regimens used in the studies. These data are considered

sufficient to allow very limited deployment of this drug in tightly controlled and supervised circumstances. In addition, development of standardised antibiotic susceptibility testing to this agent should be considered a priority, and should be developed and made available to all prescribers by a single UK reference laboratory.

Cost effectiveness of bedaquiline

No cost-effectiveness studies or evaluations were found, likely due to the fact this is a recently developed drug. However, modelling has been undertaken to compare data on the cost of the current treatment pathway for MDR-TB and XDR-TB with the cost of treatment using bedaquiline. In 2012 there were 89 cases of MDR-TB and 3 cases of XDR-TB (Public Health England, 2014). Bedaquiline (or delamanid) will only be indicated in a subset of patients within this cohort in whom it is not feasible to compose an adequate treatment regimen due to drug resistance patterns or patient's intolerance to existing antibiotics. It is estimated this will affect approximately 25% to 30% of this cohort, so between 20 to 25 patients per year in whom there is not an alternative treatment for this serious infectious disease.

Evidence base for Delamanid

Delamanid is a novel nitro-dihydro-imidazo-oxazole derivative that specifically inhibits mycolic acid biosynthesis (Matsumoto, 2006) and has been shown to have excellent activity against *Mycobacterium tuberculosis*. It is described as a pro-drug that undergoes reductive metabolism by *M. tuberculosis* to produce an active free radical. Since the *in-vitro* activity of delamanid is unaffected by mechanisms conferring resistance to isoniazid, the precise mechanism of action differs between the two agents.

Delamanid resistance has occurred during treatment and therefore it must be administered along with other drugs predicted to be effective. Mycobacterial resistance to delamanid may develop due to a mutation in one of the five coenzyme F420 genes necessary for the activation of delamanid.

Delamanid's pharmacokinetic characteristics, drug-drug interaction (DDI) potential, and short-term safety and tolerability in healthy subjects were derived from 12 Phase I trials involving 588 subjects consisting of 5 single-dose trials involving 141 subjects

receiving doses up to 400 mg delamanid, 6 multiple-dose trials with subjects receiving up to 400 mg per day for up to 14 days, and 1 multiple-dose trial where subjects received 800 mg per day for 10 days.

Two of the 12 trials used a jet milled tablet formulation (in 108 subjects) that exhibited poor absorption, 9 trials (in 474 subjects) used an alternative spray dried tablet formulation, and the remaining 1 trial used a capsule formulation containing ^{14}C-delamanid (in 6 subjects). Two phase IIA early bactericidal activity (EBA) trials were conducted in patients with uncomplicated smear-positive pulmonary TB to evaluate clinical antimycobacterial activity. An initial pilot trial used the jet milled tablet formulation (24 patients) and a subsequent, larger published trial in 54 patients using the spray dried formulation (Diacon, 2011).

Three phase IIb clinical trials have been conducted: trials 204, 208 & 116. The main evidence for the efficacy and safety of delamanid is provided in trial 204, a multi-centre (17 sites in 9 countries), randomised, double-blind, placebo controlled trial. Patients completing trial 204 had the option to enrol in trial 208, a non-randomised open-label extension study used to collect evidence of the safety and tolerability of delamanid treatment.

All patients entering trial 204, irrespective of participation in trial 208, also had the option to enrol in trial 116, an observational study to assess long term outcomes at 24 months post randomisation in trial 204. Patients continued to receive WHO recommended background regimen throughout the full duration of their MDR-TB treatment.

Trial 204 involved 481 patients (aged 18 to 65 years) with pulmonary MDR-TB randomised to receive either 100 mg twice daily delamanid (161 patients), 200 mg twice daily delamanid (160 patients) or placebo twice daily (160 patients) for 8 weeks in addition to 4 or 5 antibiotics according to WHO guidelines adjusted individually as required. The primary efficacy end point was the proportion of the subset of the modified intention-to-treat (mITT; i.e. shown to be sputum culture positive at baseline) that achieved sputum culture conversion using MGIT liquid culture medium by day 57.

A total of 402 patients were eligible for the mITT efficacy analysis (100 mg twice daily, 141 patients; 200 mg twice daily, 136 patients; placebo, 125 patients). Sputum culture conversion measured by MGIT up to day 57 was greater in the delamanid treated patients (100 mg twice daily 45.4%; 200 mg twice daily 41.9%) than in placebo treated patients (29.6%, p = 0.0083 and 0.0393 respectively).

A secondary efficacy endpoint was time to sputum culture conversion using liquid medium up to day 57; the hazard ratio for increased time to sputum culture conversion was 0.58 (95% CI: 0.39, 0.89) in the 100 mg group and 0.63 (95% CI: 0.42, 0.96) in the 200 mg group (Gler, 2012).

Analysis of final treatment outcomes of patients initially randomised in trial 204 and consenting to trial 116 (421 patients out of 481 randomised in trial 204) showed favourable outcomes in 74.5% of patients (143/192) treated with delamanid for at least 6 months compared to 55% of patients (126/229) who received either delamanid for 2 months or no delamanid (p<0.001). The reported mortality rate was lower in patients receiving delamanid for at least 6 months compared with those receiving delamanid for 2 months or no delamanid (1.0% v 8.3%; p<0.001) (Skipconoka, 2013).

Adverse events (AEs) were assessed in trials 204 and 208. Overall 887 trial participants received delamanid with 196 (22.1%) having a cumulative exposure of more than 6 months. In trial 204 similar numbers of treatment emergent adverse events (TEAEs) were observed in the delamanid treated patients compared to those treated with placebo although a dose related increase in adverse events was seen between the 100 mg and 200 mg twice daily groups.

The most commonly reported AEs in delamanid treated patients were headache, abdominal pain and insomnia. Other important AEs were anxiety, paraesthesia, tremor and QT prolongation. The main safety concern is QT prolongation.
The rate of prolonged QT interval was higher in the 200mg twice daily group (13.1%) than in the 100 mg twice daily group (9.9%), and both higher than the placebo group (3.8%) (p=0.005 and p= 0.048 respectively). QT prolongation increases slowly over time in the first 6-10 weeks of treatment and remains stable thereafter. QTc

prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A regulate the formation and metabolism of DM-6705 respectively.

In April 2014, the European Commission granted approval for the use of delamanid in the European Union (including the UK) as part of an appropriate combination regimen for pulmonary MDR-TB in adults when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.
In April 2014, WHO convened an expert group to evaluate existing evidence for the use of delamanid in addition to existing WHO recommended regimen for the treatment of MDR-TB, and to produce specific recommendations on the conditions for use (WHO, 2014). The expert group produced conditional recommendations (low confidence of estimates of effect) that delamanid may be added to a WHO-recommended regimen in adult patients with MDR-TB including those with additional resistance or intolerance to fluoroquinolones or second line injectable drugs, those with extended lesions, advanced disease and others deemed to be at high baseline risk for poor outcomes, as well as patients with XDR-TB. The population excludes patients with QT prolongation (WHO, 2014).

Critical evaluation of delamanid

The level of evidence for delamanid's efficacy and safety remains very limited to date. The safety of delamanid was reported to be similar to the placebo group and also across the dosing regimens used in the studies. These data are considered sufficient to allow very limited deployment of this drug in tightly controlled and supervised circumstances. In addition, development of standardised antibiotic susceptibility testing to this agent should be considered a priority, and should be developed and made available to all prescribers by a single UK reference laboratory.

Cost effectiveness of delamanid

No cost-effectiveness studies or evaluations are available, likely due to the fact this is a recently developed drug. However, modelling has been undertaken to compare data on the cost of the current treatment pathway for MDR-TB and XDR-TB with the cost of treatment using delamanid. Based on currently available data, in 2013 there were 74 cases of MDR-TB (86 in 2012), of which 17 cases were pre-XDR and 3

cases XDR-TB (PHE, 2014). Delamanid (or bedaquiline) is only indicated for a subset of patients within this cohort in whom it is not feasible to compose an adequate treatment regimen due to drug resistance patterns or patient's intolerance to existing antibiotics. It is estimated this will affect 25% to 30% of this cohort, so between 20 to 25 patients per year in whom there is not an alternative treatment for this infectious disease.

7 Rationale behind this policy statement

MDR-TB carries a mortality risk greater than that of drug-susceptible TB. MDR-TB is difficult to treat, requiring 18-24 months of treatment after sputum culture conversion with a regimen that consists of four to six medications (second-line drugs) with limited efficacy and significant toxicity. The need for new therapeutic options is critical.

Bedaquiline is a novel oral diarylquinoline approved by US-FDA for the treatment of adults with pulmonary MDR-TB on the basis of Phase IIb trial data under the provisions of the accelerated approval regulations for serious or life-threatening conditions. Bedaquiline, as part of an appropriate combination regimen, can shorten time to culture conversion in adult patients with pulmonary MDR-TB in whom standard MDR-TB regimens cannot otherwise be composed for reasons of resistance or tolerability. The main safety concerns of bedaquiline include QT interval prolongation, hepatic related adverse events, and excess mortality. Further evidence is needed to assess safety and efficacy.

Delamanid is a novel oral nitroimidazole authorised by the European Commission for the treatment of adults with pulmonary MDR-TB on the basis of Phase IIb trial data under the provisions for orphan medicinal products. Delamanid, as part of an appropriate combination regimen, can increase the proportion of patients achieving sputum culture conversion at 2 months in adult patients with pulmonary MDR-TB in whom standard MDR-TB regimens cannot otherwise be composed for reasons of resistance or tolerability. The main safety concern of delamanid is QT interval prolongation. Further evidence is needed to assess safety and efficacy.

8 Criteria for commissioning

Patient selection: Bedaquiline

- Bedaquiline should only be used as part of combination therapy (minimum four-drug treatment regimen), and
- Bedaquiline used for a maximum duration of 24 weeks (6 months) at a suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks);and
- Prescribed for treatment of adult (18 to 65) patients with proven (laboratory confirmed*) MDR- or XDR-TB and documented resistance to fluoroquinolones; and
- Provided as part of supervised treatment of adult (18 to 65) patients

* In exceptional circumstances, cases of non-pulmonary MDR-TB may be considered for Bedaquiline; these will be discussed on a case by case basis and in conjunction with the Regional MDT and the National MDR-TB advisory Group. In addition, when microbiological evidence is lacking but compelling circumstantial evidence indicates very likely MDR/XDR-TB aetiology (e.g. sputum smear negative active disease in a close contact of a patient with laboratory confirmed MDR/XDR-TB), then agreement may be reached by the local MDR-TB MDT and National MDR-TB advisory group to allow use despite the lack of confirmatory microbiology.

The WHO-recommended MDR-TB treatment regimen is typically composed of at least pyrazinamide and four second-line drugs considered to be effective (based on drug susceptibility testing - DST): a fluoroquinolone (preferably later-generation), a second-line injectable agent, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or p-aminosalicylic acid. Bedaquiline may be indicated if such a regimen is not feasible due to:

- *in vitro* resistance to a drug (see b); or
- known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen

Bedaquiline should only be offered to patients when the following criteria have been satisfied:

- the decision to use bedaquiline is agreed by the MDT of the MDR-TB treatment centre (see below) or the regional MDT in conjunction with a MDR-TB treatment centre and the case is submitted to the British Thoracic Society (BTS) MDR-TB Advisory Service (http://forums.brit-thoracic.org.uk);
- laboratory confirmed MDR-TB patients with strains resistant to fluoroquinolones or the second-line injectable drugs (kanamycin, amikacin, capreomycin). In these cases, bedaquiline may have a crucial role bringing the number of drugs likely to be effective to a minimum of four, strengthening the regimen and averting the acquisition of additional resistance and progression towards XDR-TB (WHO, 2013);
- bedaquiline must not be added alone to a failing regimen;
- informed consent after describing bedaquiline's toxicity profile has been obtained from the patient;
- bedaquiline is used for a maximum of 6 months (400mg daily for 2 weeks; followed by 200mg three times a week for the following 22 weeks);
- an obligatory framework is in place for monitoring QT interval prolongation or development of arrhythmia with pre-treatment ECG to determine baseline QT interval and monitoring at two weeks and then monthly over 6 months; repeat if symptomatic or after the addition of any new medication known to prolong QT (Potter et al 2014);
- caution is required if concurrent administration of drugs recognised to prolong cardiac QT interval (e.g. clofazimine, moxifloxacin or macrolides); if this is unavoidable monitor ECG after the introduction of the drug and monthly thereafter for the duration of treatment (Potter et al 2014);
- concurrent administration with CYP3A4 inducers (such as the rifamycins) is contraindicated in view of its metabolism *via* this route;
- should be used with caution when given together with drugs that inhibit liver function (e.g. ketoconazole or lopinavir/ritonavir effect on CYP3A4) as this could increase bedaquiline concentration and toxicity;
- follow the baseline and ongoing monitoring recommendations of the BTS TB drugs monograph, http://www.tbdrugmonographs.co.uk/ (Potter et al 2014);
- a mandatory reporting mechanism to the National MDR TB Advisory Service for patient outcomes for all patients receiving this drug is provided and adhered to.

Patient selection: Delamanid

- Delamanid must only be used as part of a combination therapy (minimum four-drug treatment regimen) and
- Delamanid used for a maximum duration of 24 weeks (6 months) at the recommended dosing (100 mg twice daily);
- Prescribed for treatment of adult (18 to 65) patients with proven (laboratory confirmed*) MDR- or XDR-TB
- Provided as part of supervised treatment of adult (18 to 65) patients

*In exceptional circumstances, cases of non-pulmonary MDR-TB may be considered for delamanid; these will be discussed on a case by case basis and in conjunction with the Regional MDT and the National MDR-TB advisory group. In addition, when microbiological evidence is lacking but compelling circumstantial evidence indicates very likely MDR/XDR-TB aetiology (e.g. sputum smear negative active disease in a close contact of a patient with laboratory confirmed MDR/XDR-TB), then agreement may be reached by the local MDR-TB MDT and National MDR-TB advisory group to allow use despite the lack of confirmatory microbiology.

The WHO-recommended MDR-TB treatment regimen is typically composed of at least pyrazinamide and four second-line drugs considered to be effective (based on drug susceptibility testing – DST): a fluoroquinolone (preferably later-generation), a second-line injectable agent, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or p-aminosalicylic acid. Delamanid may be indicated if such a regimen is not feasible due to:

- In vitro resistance to a drug: or
- Known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen

Delamanid should only be offered to patients when the following criteria have been satisfied:

- The decision to use delamanid is agreed by the MDT or the MDR-TB treatment centre (see below) or the regional MDT in conjunction with a MDR-TB treatment centre and the case is submitted to the British Thoracic Society (BTS) MDR-TB Advisory Service (http://forums.brit-thoracic.org.uk);
- Delamanid must not be added alone to a failing regimen;

- Informed consent after describing delamanid's safety profile has been obtained from the patient;
- Delamanid is used for a maximum of 6 months (100mg twice daily);
- An obligatory framework is in place for monitoring QT interval prolongation or development of arrhythmia with pre-treatment ECG to determine baseline QT interval and monitoring at two weeks and then monthly over 6 months; repeat if symptomatic or after the addition of any new medication known to prolong QT;
- Do not administer delamanid if serum albumin is <28 g/L; increase ECG monitoring frequency for the full delamanid treatment period in patients who start delamanid with serum albumin 2.8g/dL <3.4 g/dL or a fall into this range;
- Caution is required if concurrent administration of drugs recognised to prolong QT interval (e.g. clofazimine, moxifloxacin or macrolides); if this is unavoidable monitor ECG after the introduction of the drug and monthly thereafter for the duration of treatment;
- Concurrent use of delamanid and bedaquiline is not recommended without evidence of the absence of drug-drug interactions particularly in relation to QT interval prolongation. Caution is required if delamanid is administered after treatment with bedaquiline due to the very long (5 month) tissue half-life of bedaquiline. If use of delamanid is unavoidable, enhanced ECG monitoring should be implemented;
- Concurrent administration of strong CYP3A inducers (e.g. carbamazepine) is contraindicated in view of delamanid's metabolism via this route;
- Caution is required in patients with known cardiac risk factors for QT interval prolongation (e.g. Known congenital QTc-interval prolongation or any condition known to prolong QTc interval or QTc > 500 ms; history of symptomatic cardiac arrhythmias or clinically relevant bradycardia; any predisposing cardiac conditions for arrhythmia; electrolyte disturbances; medicinal products known to prolong QTc interval);
- Follow the baseline and ongoing monitoring recommendations of the BTS TB drugs monograph, http://www.tbdrugmonographs.co.uk;
- A mandatory reporting mechanism to the National MDR-TB Advisory Service for patient outcomes for all patients receiving delamanid is provided and adhered to.

MDR-TB Centres

MDR-TB Centres are TB treating centres with established experience and expertise in managing and supporting patients with MDR- and XDR-TB. MDR-TB Centres should generally fulfil the following criteria:

- regional tertiary referral units with dedicated negative pressure rooms and outpatients facilities;
- annual case load of at least 50 TB index cases;
- on site or formal links with, and rapid access to, specialist paediatric and HIV services;
- formal links to a thoracic surgical unit;
- access to rapid molecular diagnostics;
- ability to offer IV antibiotics to outpatients;
- dedicated outreach and DOT service;
- has a multi-disciplinary team (MDT) with representation from the Centre's microbiology and pharmacy teams.

MDR-TB Centres should maintain a register of all patients receiving bedaquiline or delamanid, including documented resistance to antimycobacterial drugs, current treatment regime, results of regular monitoring of liver function and ECG; sputum smear results; side effects, social risk factors. Patients receiving bedaquiline or delamanid should be managed at MDR-TB Centres or co-managed by MDR-TB Centres and local TB treatment centres. The MDR-TB Centre will provide the prescription and case review at agreed critical points (at least 2 months, 4 months and 6 months; this may be done via a regional MDT in exceptional circumstances); the local centres (or MDR-TB treatment centres) will provide routine case management, DOT, monitoring of treatment and adverse reactions, patient support and outreach.

Cost

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England

may need to review whether the policy remains affordable and may need to make revisions to the published policy.

9 Patient pathway

Patients with MDR-TB or XDR-TB requiring bedaquiline or delamanid will only be managed at a recognised MDR-TB Centre after approval by the MDR-TB Advisory Service or the local MDT.

Patients could be co-managed by an MDR-TB Centre (who will provide the prescription) and local units with established experience and expertise in treating MDR-TB patients. Units will follow WHO recommended regimens and will have access to adequate outreach and laboratory support.

10 Governance arrangements

Bedaquiline and delamanid treatments should be administered under closely monitored conditions, adhering to best practice in treatment delivery, to enable optimal drug effectiveness and safety. Bedaquiline and delamanid should only be used with clinical expert consultation as part of combination therapy (minimum four-drug treatment regimen) and administered by direct observation (DOT) to adults aged ≥18 years with a confirmed diagnosis of MDR- or XDR-TB. Oversight of the treatment and management programme will be provided by the local recognised MDR TB centre and the case submitted to the National MDR Advisory Service - an independent group of experts in clinical management and public health (Potter et al, 2014).

11 Mechanism for funding

Funding to the provider will be in accordance with their agreed tariff arrangements.

12 Audit requirements

Further evidence is needed to assess safety and efficacy. All patients treated with bedaquiline or delamanid for MDR-TB or XDR-TB should be included in a national register. The register will be held by the BTS MDR-TB advisory service. Data should

include baseline information on disease severity, treatment history, documented resistance to anti-TB drugs, as well as patients' response to bedaquiline or delamanid including culture conversion and monitoring of side effects, in particular QT interval and liver function.

MDR-TB centres will be expected to audit the use of bedaquiline and delamanid as outlined in this policy.

13 Documents which have informed this policy

See references.

14 Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

15 Date of review

This policy will be reviewed in 2016/17 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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