Clinical Commissioning Policy Statement: Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid

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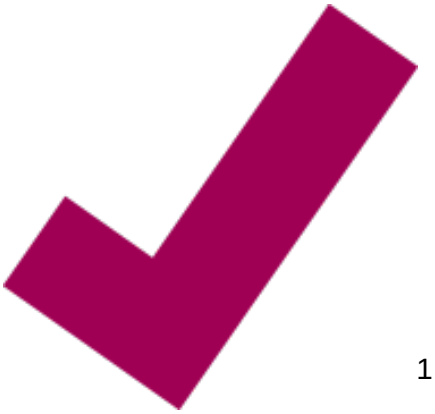

Clinical Commissioning Policy Statement: Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid

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Policy Statement

NHS England will commission Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid in accordance with the criteria outlined in this document.

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 this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB)

TB is a disease caused by the bacteria *Mycobacterium tuberculosis*, which mainly affects the lungs, but can be present in other areas of the body. Multidrug-resistant tuberculosis (MDR-TB) is when the TB bacteria fail to respond to a combination of two of the four main antibiotics (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 ineffective or incomplete treatment. Extensively drug-resistant tuberculosis (XDR-TB) is a form of TB that is resistant to at least four of the main anti-TB drugs (rifampicin, isoniazid, fluoroquinolones and second-line injectable agents).

About current treatments

An MDR-TB regimen is typically composed of at least four second-line drugs considered to be effective (based on drug susceptibility testing): a fluoroquinolone (preferably later-generation) and three other antibiotics in line with current WHO guidelines, giving preference to oral regimens. Currently adults (aged 18-65 years) can have bedaquiline or delamanid as part of this combination therapy for up to six months if they meet the criteria set out in the current clinical commissioning policy (NHS Commissioning Board, 2015).

About the new treatment

Bedaquiline is a type of antibiotic that is used to treat MDR-TB. Antibiotics are medicines that kill bacteria that cause disease. It must always be taken together with other medicines for treating tuberculosis. The combination of drugs is called a regimen.

Bedaquiline has been shown to reduce the time to culture conversion which is when samples taken from a patient with tuberculosis do not grow the bacteria that causes

tuberculosis in a laboratory. This is an indication of effective treatment for tuberculosis and that the patient is recovering from tuberculosis.

Delamanid is another antibiotic for the treatment of tuberculosis caused by bacteria that are not killed by the most commonly used antibiotics to treat tuberculosis. It also needs to be given in combination with other drugs to treat MDR-TB and has also been shown to reduce the time to culture conversion in adults with MDR-TB.

This updated policy reflects the recommendations of the 2018 WHO guidelines for MDR-TB and XTR-TB. Some of the recommendations sit outside of the current licenses for bedaquiline and delamanid but are supported by a number of studies.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with MDR-TB and XDR-TB with: bedaquiline, for those aged 6 years and over; delamanid, for those aged 3 years and/or 30kg or more; the extended (>6 months) and/or sequential use of bedaquiline and delamanid for adults, including those aged 65 years and over. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

Tuberculosis (TB) is an infectious disease that continues to present a significant public health problem in England and world-wide. England has one of the highest incidence rates of TB within Western European countries and there is great variation in the distribution of the disease across population sub-groups (PHE, 2018).

Without treatment TB can be fatal, while those who survive without treatment can experience long-term health problems and remain infectious so put others at risk through on-going community transmission.

MDR-TB is when the TB bacteria fail to respond to two of the four antibiotics usually used for treatment (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. XDR-TB is a form of TB that is resistant not only to rifampicin and isoniazid but also two other MDR-TB drugs (fluoroquinolones and injectable drugs (kanamycin, amikacin and capreomycin)). In addition, 'functional' MDR-TB or XDR-TB may arise when a patient is intolerant of some of the TB medications. Intolerance may present as, for example, thrombocytopaenia, optic neuritis, peripheral neuropathy, intractable vomiting or prolonged QT interval. A World Health Organization (WHO) recommended regimen cannot then be constructed so alternative anti-TB drug(s) is/are required to continue with treatment (WHO, 2018).

The treatment of MDR-TB is difficult, expensive and longer than the usual TB treatment regimen of six months, requiring administration of numerous drugs, many of which are only partially effective. On a world-wide scale, outcomes are poor, with successful treatment completion rates of 55% (WHO, 2016).

The latest WHO guidelines have changed the classification of MDR-TB drugs and provide principles for the design of MDR-TB treatment regimens (WHO, 2018). According to this classification, anti-TB drugs are grouped into three classes. At least four drugs should be given initially, and preference should be given to the three drugs in group A (which include a fluoroquinolone and bedaquiline), then one or both

of the two drugs from group B, then, if necessary, drugs from group C (which include delamanid). Injectable agents have now been moved to group C (amikacin) or removed completely (capreomycin and kanamycin) as fully oral regimens are preferred, especially given the significant toxicity and lesser efficacy of the injectable agents (Arnold *et al.* 2017; Ahmad *et al.* 2018). Thereafter, at least three oral drugs should be continued until a total duration of 18-20 months. For some patients with MDR-TB or XDR-TB, these current treatments are not viable as it difficult to compose an initial regimen with at least four drugs or three drugs in a continuation regimen due to intolerance or resistance. As a result, some patients may be administered regimens which are less effective and are associated with more severe adverse events. To be able to construct a suitable regimen for these patients, it may be necessary for bedaquiline or delamanid to be administered for extended periods of time or sequentially.

Compared to adults, children with TB infection are at higher risk of disease progression if preventive therapy is not given. However, if diagnosed and treated, treatment outcomes are better than for adults. The WHO 2018 guidance states bedaquiline may be used for patients aged 6-17 years and delamanid for children aged 3 years or more as part of a longer MDR-TB regimen (WHO, 2018).

Currently, bedaquiline and delamanid are commissioned for use individually but not sequentially for patients with MDR-TB and XDR-TB and only for a maximum of six months duration in adults aged 18-65 years (NHS Commissioning Board, 2015).

Bedaquiline is a novel oral diarylquinoline anti-microbial agent with a unique mechanism of action: the specific and selective inhibition of mycobacterial ATP synthase, essential for energy generation in M. tuberculosis. It has been shown to be effective in reducing the time to negative sputum culture conversion in adult patients with MDR-TB (Diacon et al., 2014).

Delamanid is a novel oral nitroimidazole and 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. It has been shown

to be effective in increasing the proportion of MDR-TB patients achieving sputum culture conversion after eight weeks of treatment (Diacon *et al.*, 2011).

This policy statement confirms that bedaquiline and delamanid are to be made available in line with 2018 WHO guidance. Thus, bedaquiline should be made available to patients aged 6 years and over, and delamanid to patients aged 3 years and/or 30kg or more. These drugs should be given for the necessary time and sequentially, if required, as determined on a case by case basis. Additional clips may be inserted to improve the MR reduction.

From 1st January 2021, following the end of the transition period for the withdrawal of the United Kingdom from the European Union, Deltyba® (delamanid) 50mg film-coated tablets will cease to be a licensed medicine in Great Britain.

2 Definitions

Drug-susceptible TB: TB caused by a strain of M. tuberculosis that is susceptible to both isoniazid and rifampicin, although it might be resistant to other anti-TB drugs.

Multi-drug resistant TB (MDR-TB): TB caused by a strain of M. tuberculosis that is resistant to both isoniazid and rifampicin, the two most important first-line drugs to treat TB.

Extensively-drug resistant TB (XDR-TB): Disease caused by MDR strains of M. tuberculosis that are resistant to at least one of the previous second-line injectable drugs (amikacin, kanamycin, capreomycin) and any fluoroquinolone.

Pre-XDR-TB: Disease caused by MDR strains of M. tuberculosis that are resistant to either one of the previous second-line injectable drugs (amikacin, kanamycin, capreomycin) or a 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.

Cure: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase (WHO Guidelines 2018)

3 Aims and Objectives

This policy statement considered: the use of bedaquiline in patients aged 6 years and over, and delamanid in patients aged 3 years and over; and the extended (>6 months) and/or sequential use of bedaquiline and delamanid in adult patients, including patients aged 65 years and over, for the treatment of MDR-TB and XDR-TB.

- The objectives were to: Establish the clinical effectiveness, safety and cost-effectiveness of bedaquiline in patients aged 6 years and over, and delamanid in patients aged 3 years and over; and the extended (>6 months) and/or sequential use of bedaquiline and delamanid in adult patients, including patients aged 65 years and over.
- Identify the clinical criteria to be used to identify suitable patients to be considered for the use of bedaquiline in patients aged 6 years and over, and delamanid in patients aged 3 years and over; and the extended (>6 months) and/or sequential use of bedaquiline and delamanid in adult patients, including patients aged 65 years and over.
- Define commissioning arrangements required for the use of bedaquiline in patients aged 6 years and over, and delamanid in patients aged 3 years and/or 30kg or more; and the extended (>6 months) and/or sequential use of bedaquiline and delamanid in adult patients, including patients aged 65 years and over.

4 Epidemiology and Needs Assessment

In 2017, the number of new cases or cases of TB that returned in England was 5,102, which is the lowest it has been since 1990. The incidence rate was 9.2 per

100,000, which now makes England a low incidence country, by WHO definition. However, the proportion of people with the MDR form of TB (1.8%) has not decreased since 2014. Over half (55.2%) of the TB cases in 2017 were aged 15 to 44 years old and the lowest rate of TB was seen in children; there are similar proportions of patients with MDR or rifampicin resistant TB (RR-TB) between these age groups (PHE, 2018).

55 people were diagnosed with MDR-TB or RR-TB in England in 2017, three of whom were diagnosed with XDR-TB. In 2017, 62% of patients with TB had a diagnosis confirmed by growing the bacteria in a laboratory; 8.5% of these people had resistance to at least one first line drug and 1.4% had MDR-TB (PHE, 2018).

TB rates in England are significantly affected by social risk factors (SRFs). SRFs for TB include alcohol or drug misuse, homelessness and imprisonment. For example, in 2017 the proportion of patients with MDR/RR-TB was almost two times higher in people with an SRF (2.7%) compared to those without an SRF (1.5%). In 2017, 12.6% of people diagnosed with TB had an SRF. Other sub-groups who are more frequently diagnosed with TB include new migrants from countries where TB is more common and ethnic minority groups (PHE, 2018).

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support routine commissioning of this treatment for the indication.

Evidence review summary for the extended (>6 months), sequential and/or concomitant use of bedaquiline and delamanid in adults:

- There is little research within scope of the questions identified for this review. Six studies were found that were suitable for inclusion.

PICO I: Bedaquiline use for over 6 months

One unrandomised controlled trial (Guglielmetti et al 2017, n=45) and one systematic review and meta-analysis (WHO 2016)

Cure

- Guglielmetti et al 2017 reported a cure rate after less than 190 days bedaquiline (dose not reported) of 7/12 (58%) and after more than 190 days bedaquiline (dose not reported) of 27/33 (82%), p=0.13. The authors do not define cure, but usually cure of TB means that that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Treatment completion

- Guglielmetti et al 2017 reported a treatment completion rate after less than 190 days bedaquiline (dose not reported) of 2/12 (17%) and after more than 190 days bedaquiline (dose not reported) of 0/33 (0%), p=0.067. The authors do not define treatment completion, but usually it occurs when treatment is completed but there are fewer than five cultures performed during the last 12 months.

Mortality

- Guglielmetti et al 2017 reported a mortality rate after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 1/33 (3%), p=1.0.

Treatment failure

- Guglielmetti et al 2017 reported a treatment failure rate after less than 190 days bedaquiline (dose not reported) of 1/12 (8%) and after more than 190 days bedaquiline (dose not reported) of 2/33 (6%), p=1.0. The authors do not define treatment failure, but usually it means that a patient had two or more positive cultures among five collected during the final 12 months of treatment or had a positive culture among the final three sputum cultures collected.

Median time to sputum smear conversion

- Guglielmetti et al 2017 reported a median time to sputum smear conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 110 days, p=0.002. Time to sputum smear conversion is the elapsed time between treatment

starting and the first sputum sample free of TB on microscopy.

Median time to sputum culture conversion

- Guglielmetti et al 2017 reported a median time to sputum culture conversion after less than 190 days bedaquiline (dose not reported) of 71 days and after more than 190 days bedaquiline (dose not reported) of 91 days, p=0.021. Time to sputum culture conversion is the elapsed time between treatment starting and the first sputum sample free of TB on culture.

Odds of culture conversion

- Guglielmetti et al 2017 do not report an odds ratio comparing less than 190 days bedaquiline (dose not reported) and more than 190 days bedaquiline (dose not reported), but state that p=0.702. The odds of culture conversion after multivariate adjustment indicate whether treatment duration is associated with the probability of TB being cultured from a sputum sample, adjusting for potential confounders. The authors do not report which potential confounders they selected for adjustment.

Severe adverse effects

- Guglielmetti et al 2017 reported a rate of severe adverse effects after less than 190 days bedaquiline (dose not reported) of 5/12 (42%) and after more than 190 days bedaquiline (dose not reported) of 23/33 (70%), p=0.163. Severe adverse effects are defined in this study as those causing severe, life-threatening or fatal effects.

Prolongation of the corrected QT interval

- Guglielmetti et al 2017 reported a rate of prolongation of the corrected QT interval after less than 190 days bedaquiline (dose not reported) of 0/12 (0%) and after more than 190 days bedaquiline (dose not reported) of 5/33 (15%), p=0.303. Prolongation of the corrected QT interval is an electrocardiographic abnormality associated with bedaquiline and delamanid.
- The WHO (2016) systematic review included data on patients treated with bedaquiline for more than six months. Because this evidence was “limited”,

WHO recommended that use of bedaquiline be for six months only.

- We found no evidence about the cost-effectiveness or subgroup effects of bedaquiline used for more than six months.

Conclusion

- The available evidence does not indicate better results from use of bedaquiline beyond six months, the maximum specified in the drug's license.

PICO II: Delamanid use for over 6 months

Two unrandomised controlled trials (Kuksa et al 2017, n=19 and Skripconoka et al 2013, n=421) and one case series (Chang et al 2018, n=11).

Cure

- Chang et al 2018 reported a cure rate after delamanid 200mg/day for a median of 12 months (range 6 to 22 months) of 9/11 (82%). The authors did not define cure.
- Kuksa et al 2017 reported a cure rate after delamanid (dose not reported) for more than 26 weeks of 9/9 (100%) and after delamanid (dose not reported) for 26 weeks or less of 7/7 (100%), p=1.0. The authors define cure as meaning that treatment was completed as recommended without failure and three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.
- Skripconoka et al 2013 reported a cure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 110/192 (57.3%, 95% confidence interval (CI) 50.0% to 64.4%), and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 111/229 (48.5%, 95% CI 41.8% to 55.1%), p≥0.05. Prescription of delamanid for two months is outside the product license, which is for treatment courses of 24 weeks' duration. The authors define cure as meaning that treatment was completed with at least five consecutive negative cultures during the last 12 months

Treatment completion

- Skripconoka et al 2013 reported a treatment completion rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 33/192

(17.2%, 95% CI 12.1% to 23.3%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 15/229 (6.6%, 95% CI 3.7% to 10.6%), p<0.001. The authors define treatment completion as meaning that the participant finished all courses of drug therapy recommended but had fewer than five cultures performed during the last 12 months.

Mortality

- Skripconoka et al 2013 reported a mortality rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 2/192 (1.0%, 95% CI 0.1% to 3.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 19/229 (8.3%, 95% CI 5.1% to 12.7%), p<0.001.

Treatment failure

- Skripconoka et al 2013 reported a treatment failure rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 32/192 (16.7%, 95% CI 11.7% to 22.7%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 26/229 (11.4%, 95% CI 7.6% to 16.2%), p≥0.05. The authors define treatment failure as meaning that the participant had two or more positive cultures among five collected during the final 12 months, or a positive culture among the final three sputum cultures collected from the patient.

Default from treatment

- Skripconoka et al 2013 reported a treatment default rate after delamanid 100mg twice daily and/or 200mg twice daily for 6 or 8 months of 15/192 (7.8%, 95% CI 4.4% to 12.6%) and after delamanid 100mg twice daily or 200mg twice daily or placebo for 2 months of 58/229 (25.3%, 95% CI 19.8% to 31.5%), p<0.001. The authors define treatment default as meaning that treatment was interrupted for more than two consecutive months for any reason without medical approval.
- We found no evidence about the safety, cost-effectiveness or subgroup effects of delamanid used for more than six months.

Conclusion

- For two outcomes (cure and treatment failure), there were no significant differences between those who had had delamanid for no more than two months or had had a placebo, versus those who had received the drug for six or eight months, nor between those who had delamanid for more than 26 weeks, versus those with 26 weeks' treatment or less.
- Longer-term treatment was more often associated with treatment completion, lack of default from treatment and survival. However, this result is unreliable. The participants who received short-term treatment only did so because they did not enter the second or third studies included within Skripconoka at al 2013's analysis, leaving the research programme after only two months. The authors report no data comparing these participants with those who entered the later studies. If these participants had more severe TB or had a worse prognosis for some other reason, such as homelessness or social exclusion, that might explain both their non-participation in the second study and their worse rates of treatment completion, default and survival. These possible associations cast doubt on the reliability of the study by confounding the relationship between long-term treatment with delamanid and better outcomes and mean the former may not be the cause of the latter.
- For this reason, Skripconoka et al 2013 cannot be interpreted as indicating advantages from use of delamanid beyond six months. Kuksa et al 2017 is similarly inconclusive. Chang et al 2018 is uncontrolled and hence can shed no light on the relative effectiveness of regimens of different duration.

PICO III: Bedaquiline and delamanid combined use for over 6 months

One case series (Guglielmetti et al 2018, n=3).

Cure

Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Sputum culture conversion

- Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 3/3 (100%). Sputum culture conversion is the disappearance of TB from cultures of sputum.

Prolongation of the corrected QT interval

- Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) and delamanid (dose not reported, treatment period variable) of 2/3 (67%).
- We found no evidence about the cost-effectiveness or subgroup effects of bedaquiline and delamanid combined use.

Conclusion

- These data are far too limited to provide any useful information on the effectiveness and safety of combined use of bedaquiline and delamanid.

PICO IV: Bedaquiline and delamanid sequential use

One case series (Guglielmetti et al 2018, n=2).

Cure

- Guglielmetti et al 2018 reported a cure rate after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 2/2 (100%). The authors do not define cure, but usually it means that treatment was completed with at least five consecutive negative cultures during the last 12 months.

Sputum culture conversion

- Guglielmetti et al 2018 reported a sputum conversion rate after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 1/1 (100%).

Prolongation of the corrected QT interval

- Guglielmetti et al 2018 reported a rate of prolongation of the corrected QT interval of more than 500ms after bedaquiline (dose not reported, treatment period variable) followed by delamanid (dose not reported, treatment period variable) of 0/2 (0%).
- We found no evidence about the cost-effectiveness or subgroup effects of bedaquiline and delamanid sequential use for more than six months.

Conclusion

- These data are far too limited to provide any useful information on the effectiveness and safety of sequential use of bedaquiline and delamanid.

PICO V: Delamanid and Bedaquiline sequential use

- We found no evidence relevant to the scope of this PICO and questions.

Overall conclusions

- We found no reliable evidence to support any extension in the use of bedaquiline or delamanid beyond their product licenses.

Evidence review summary for the individual and concomitant use of bedaquiline and delamanid in children:

- There is little published research within the scope of the questions identified for this review. We found three studies suitable for inclusion.

PICO I: Bedaquiline

One case series (Achar et al 2017, n=27) Negative sputum culture results

- Achar et al 2017 reported that 23/23 (100%) of participants had negative culture results at the time the paper was prepared. 10/27 (37%) of participants were culture-negative at inception.

Electrocardiographic abnormalities

- Achar et al 2017 reported that 5/27 (19%) of participants had a corrected QT interval of more than 500ms, or more than 60ms change from baseline plus

torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. No patient experienced symptoms attributable to prolongation of QTcF during treatment with bedaquiline.

PICO II: Delamanid

One case series (Tadolini et al 2016, n=16)

Negative sputum culture results

- Tadolini et al 2016 reported that 13/16 (81%) of participants had negative culture results at the time the paper was prepared. All had positive sputum culture when delamanid was started.

Adverse effects other than "mild"

- Tadolini et al 2016 reported that 1/16 (6%) had adverse effects other than "mild".

PICO III: Bedaquiline and delamanid

One systematic review (D'Ambrosio et al 2017).

D'Ambrosio et al 2017 was a systematic review of studies reporting the results of bedaquiline and/or delamanid use in children or adolescents with confirmed MDR- or XDR-TB. It included no evidence about the concurrent use of bedaquiline and delamanid.

6 Criteria for Commissioning

Commissioning position

The evidence review found no randomised trials on the use of bedaquiline in patients aged 6 years and over, and delamanid in patients aged 3 years and/or 30kg or more; and the extended (>6 months) and/or sequential use of bedaquiline and delamanid in adult patients, including patients aged 65 years and over, for the treatment of MDR-TB and XDR-TB. However, the available evidence for the extended (>6 months) use of bedaquiline or delamanid shows acceptable outcomes with respect to cure, treatment completion and adverse effects in adults; especially considering current alternative treatments may not have been viable or as effective for these patients, due to patients not being able to tolerate the treatments or the TB being resistant to them. The 2018 update of the WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis has been used to inform this policy in conjunction with the evidence review. This has been used to determine the age range defined in the policy because the WHO evidence review incorporated additional interim results from studies in children, that are still ongoing, to construct their guidelines. These results would not have come into the scope of the NHS England evidence review because they are not yet published, peer-reviewed papers. MDR-TB poses a significant public health risk because although the number of people newly diagnosed with TB has decreased in previous years, the proportion of people with MDR-TB has not (PHE, 2018). Widening the availability of these drugs for children will provide a public health benefit as they are more effective, easier to administer and have less severe side effect profile than current alternative treatments.

Patient eligibility criteria

As a group A drug, bedaquiline is indicated for 6 months of treatment as part of an initial regimen in all MDR-TB patients (WHO, 2018). Delamanid may be used in the initial regimen if a patient has pre-XDR/XDR or if a WHO recommended regimen cannot be constructed.

WHO guidance states that bedaquiline or delamanid would not normally be continued beyond 6 months and that prescribers should follow best practice in ‘off-label’ use if the drugs are used for longer than 6 months (WHO, 2018). Based on the

evidence reviewed for this policy, NHS England have decided that adult patients may be eligible for treatment with bedaquiline or delamanid for longer than 6 months and/or sequentially if they meet any of the following criteria:

1. Laboratory confirmed MDR/XDR-TB with resistance to fluoroquinolones or the injectable drugs (kanamycin, amikacin, capreomycin)
2. Where 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). These will be discussed on a case by case basis and in conjunction with the Regional MDT and approved by the regional PHE lead.
3. Inability to construct a WHO recommended MDR-TB regimen EITHER through phenotypic or genomic defined resistance pattern OR because of intolerance/ drug interactions (functional MDR or functional XDR-TB).

Treatment starting criteria

In order to receive treatment with bedaquiline or delamanid, all of the following criteria must also be satisfied:

- The case must be discussed, and treatment agreed with the MDT of the MDR- TB treatment centre (see patient pathway below) or the regional MDT in conjunction with an MDR-TB treatment centre; paediatric cases must also be discussed and their treatment agreed by the Paediatric Infectious Diseases Centre.
- The patient must be managed under directly observed therapy
- Bedaquiline or delamanid should be used as part of combination therapy in line with WHO-recommended MDR-TB treatment regimens considering:
    - in vitro resistance to a drug or
    - known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen
- The WHO-recommended MDR-TB treatment regimen is as described in the latest WHO treatment guidelines for drug-resistant tuberculosis (currently 2018) – see below.

Recommended dosing for adults (age 18+ years) (taken from: http://www.tbdrugmonographs.co.uk/):

- Bedaquiline: 400 mg daily for the first 2 weeks, followed by 200 mg three times per week
- Delamanid: 100 mg twice daily.

Recommended dosing for bedaquiline in children (age 6+ years), by weight (taken from: The Sentinel Project, 2019):

- 1-15kg: Consult with a specialist
- 16-23kg: 200 mg daily for the first 2 weeks, followed by 100 mg three times per week
- 24-30kg: 200 mg daily for the first 2 weeks, followed by 100 mg three times per week
- 31-34kg: 400 mg daily for the first 2 weeks, followed by 200 mg three times per week
- >34kg: 400 mg daily for the first 2 weeks, followed by 200 mg three times per week

Recommended dosing for delamanid in children (age 3+ years and/or 30kg or more), by weight:

- 30-49kg: 50 mg twice daily
- 50kg or above: 100 mg twice daily

Safety Criteria

The following safety criteria must be adhered to for any regimen containing bedaquiline or delamanid:

- An obligatory framework must be 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 (TB Drug Monographs, 2018).
- If delamanid is administered sequentially after treatment with bedaquiline, then an enhanced ECG monitoring should be implemented as bedaquiline

has a very long (five month) tissue half-life. Weekly for 1 month then monthly thereafter.

- Caution is required if concurrent administration of drugs recognised to prolong cardiac QT interval (e.g. clofazimine, moxifloxacin, neuroleptics and some anti-emetics); if this is unavoidable monitor ECG after the introduction of the drug and monthly thereafter for the duration of treatment (http://www.tbdrugmonographs.co.uk);
- The baseline and ongoing monitoring recommendations of the TB drug monograph, (http://www.tbdrugmonographs.co.uk) must be followed.
- Provider organisations must register all patients using software such as Blueteq and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.
- Special caution should be applied when treating those aged over 65 years to ensure that any current medications or co-morbidities are considered.
- All clinicians prescribing these drugs should refer to the current summaries of product characteristics (SPCs).

In addition to those criteria listed above, the following safety criteria must be adhered to for any regimen containing bedaquiline:

- Concurrent administration of bedaquiline with CYP3A4 inducers (such as the rifamycins) is contraindicated in view of its metabolism via this route.
- Bedaquiline should be used with caution when given together with drugs that inhibit liver enzyme function (e.g. ketoconazole or lopinavir/ritonavir effect on CYP3A4) as this could increase bedaquiline concentration and toxicity.

In addition to those criteria listed above, the following safety criteria must be adhered to for any regimen containing delamanid:

- 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 to 3.4 g/dl or fall into this range;
- 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).

Continuation of treatment:

- Treatment of adults with bedaquiline or delamanid should not continue beyond 24 months.
- Treatment of children with bedaquiline or delamanid for longer than 6 months and/or sequentially is not recommended within this policy.
- Response to treatment will be monitored by culture and smear conversion and imaging (chest X-ray) and drug sensitivity or molecular sensitivity testing will be used to check for resistance. These results will determine if the patient stays on the current treatment regimen, or a change is required.
- Bedaquiline is used as a first line drug as part of an MDR TB regimen as recommended by WHO 2018 guidance. Delamanid may be used as a third line drug as expertly advised and in line with WHO guidance.
- Bedaquiline or delamanid **must not** be added alone to a failing regimen.
- Bedaquiline or delamanid may be used for a maximum duration of 24 weeks (six months) in the first instance. Treatment must be reviewed at least every six months and any extension(s) (up to six months at a time) must be agreed with the Centre and Regional MDT and submitted with justification through the prior approval system. Reasons for use beyond six months may include delayed microbiological response, weak treatment regimens due to intolerance or drug resistance and/or individual risk factors for poor outcomes.
- Combined use of bedaquiline with delamanid is not recommended within this policy.

Treatment stopping criteria

Treatment will be stopped in the following instances:

- A patient is cured (as defined in the treatment guidance (WHO, 2018)).

- Maximum duration of treatment of up to 24 months is reached.
- Toxicity or serious side effects caused by bedaquiline or delamanid
- Sustained QT interval prolongation to ≥ 500ms or the development of a significant arrhythmia
- Patients are not complying with directly observed therapy.

Treatment stopped due to serious side effects, toxicity or safety concerns can potentially be reinstated once these have been addressed.

7 Patient Pathway

Patients with MDR- and XDR-TB should be referred to MDR-TB centres as defined below.

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 fulfil the following criteria:

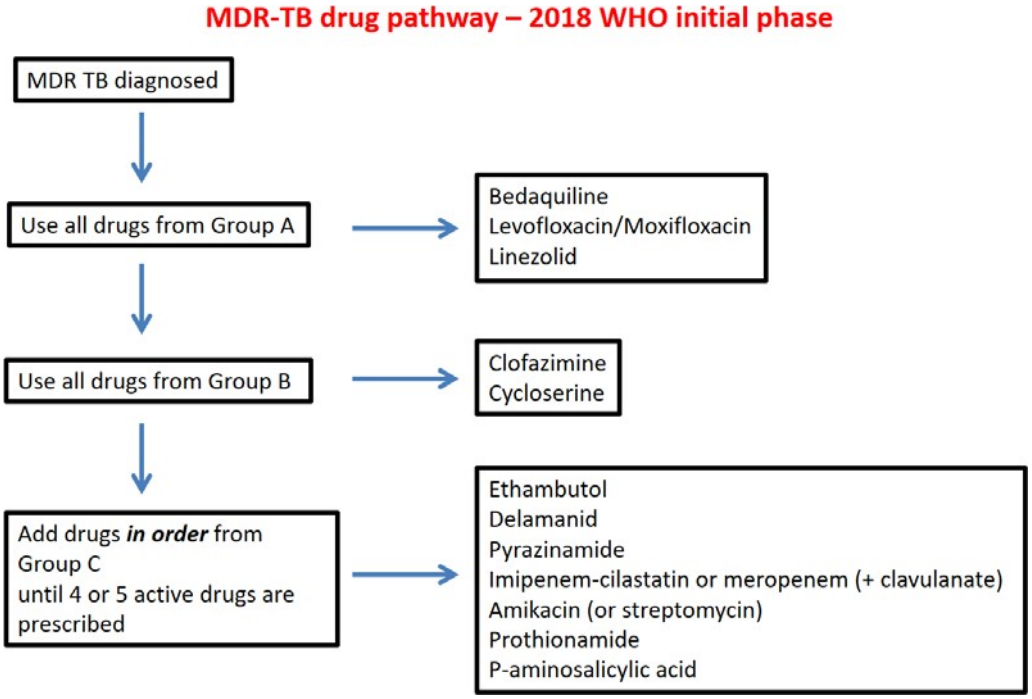
- Tertiary referral units with dedicated negative pressure rooms and outpatients' facilities;
- Annual case load of at least 50 TB index cases;
- On site or formal links with, and rapid access to, specialist paediatric and HIV services;
- Formal links to a thoracic surgical unit;
- Access to rapid molecular 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/Paediatric Infectious Diseases services should maintain a register of all patients receiving bedaquiline or delamanid, including documented resistance

to anti-mycobacterial drugs, current treatment regimen, results of regular monitoring of liver function and ECG; sputum smear results; side effects, social risk factors.

The MDR-TB Centre/Paediatric Infectious Diseases services will provide the prescription and case review at agreed critical points (at least 2 months, 4 months, 6 months, 12 months, 18 months and 24 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.

Treatment should follow the algorithm described below:



This grouping of drugs is in accordance with the classification of MDR-TB drugs in the WHO guidelines and should be used as the principle for regimen design in adults, see below footnotes 1-9 relating to the WHO grouping of medicines (WHO, 2018). This same grouping of drugs should also be used as the principle for regimen design in children, excluding bedaquiline in children aged less than 6 years, and delamanid in children aged less than 3 years (WHO, 2018). There are limited data for the use of bedaquiline and delamanid in children so refer to The Sentinel Field Guide for updated treatment algorithms (The Sentinel Project, 2019).

[For info: Footnotes 1-9 from WHO 2018 guidelines - Grouping of Medicines table (WHO, 2018):

1. This algorithm is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized). Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 IPD-MA for longer regimens included no patients on thioacetazone (T) and too few patients on gatifloxacin (Gfx) and high-dose isoniazid (Hh) for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies.
2. Evidence on the safety and effectiveness of bedaquiline (Bdq) beyond 6 months and below the age of 6 years was insufficient for review. Use of Bdq beyond these limits should follow best practices in ‘off-label’ use.
3. Evidence on the concurrent use of Bdq and delamanid (Dlm) was insufficient for review.
4. Use of linezolid (Lzd) for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using Lzd for the whole duration of treatment would optimise its effect (about 70% of patients on Lzd with data received it for more than 6 months and 30% for 18 months or the whole duration). No patient predictors for early cessation of Lzd could be inferred from the IPD sub-analysis.
5. Evidence on the safety and effectiveness of Dlm beyond 6 months and below the age of 3 years was insufficient for review. Use of Dlm beyond these limits should follow best practices in ‘off-label’ use.
6. Pyrazinamide is only counted as an effective agent when DST results confirm susceptibility.
7. Every dose of imipenem-cilastatin (Imp-Cln) and meropenem (Mpm) is administered with clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or Mpm.

Amikacin (Am) and streptomycin (S) are only to be considered if DST results confirm susceptibility and high-quality audiometry monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (S resistance is not detectable with 2nd line molecular line probe assays and phenotypic DST is required). Kanamycin (Km) and capreomycin (Cm) are no longer recommended for use in MDR-TB regimens.
These agents only showed effectiveness in regimens without Bdq, Lzd, clofazimine or Dlm, and are thus only proposed when other options to compose a regimen are not possible.

8 Governance Arrangements

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using software such as Blueteq as the prior approval system and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

9 Mechanism for Funding

The funding and commissioning of these drugs will continue to be managed through the relevant local NHS England Specialised Commissioning Team and in line with the treatment criteria included within this policy.

10 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 recorded and reported using software such as Blueteq. 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 (especially for treatment durations >6 months and in children) 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.

11 Documents which have informed this Policy

This document updates and replaces Clinical Commissioning Policy: Bedaquiline and Delamanid for defined patients with MDR-TB and XDR-TB.

NHS England (2015). *Clinical Commissioning Policy: Bedaquiline and Delamanid for defined patients with MDR-TB and XDR-TB.* NHS England. Accessed 22 January 2019: <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/f04pa-bedaquiline-delamanid-oct15.pdf>.

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2019: <https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf >.

12 Date of Review

This document will be reviewed when information is received which indicates that the policy statement requires revision.

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World Health Organization (2016). Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: a review of available evidence.

Appendix A

Change form for published Specifications and Products developed by Clinical Reference Group (CRGs)

Product name: Treatment for defined patients with MDR-TB and XDR-TB including bedaquiline and delamanid

Publication number: Formerly 170132P

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
N/A	From 1st January 2021, following the end of the transition period for the withdrawal of the United Kingdom from the European Union, delamanid (Deltyba®) 50mg film-coated tablets will cease to be a licensed medicine in Great Britain	Added text as the final paragraph in Section 1 – Introduction.	Delamanid, a drug within the policy will no longer be a licensed medicine in Great Britain from 1st January 2021	Head of Clinical Policy Team (reviewed by Specialised Commissioning Pharmacy Lead)	26/11/2020
and over	and/or 30kg or more	Amended text in the second last paragraph of the introduction.	Included weight as per the licence	Head of Clinical Policy Team (reviewed by Specialised Commissioning Pharmacy Lead)	26/11/2020
and over	and/or 30kg or more	Amended last sub paragraph of the aims and objectives.	Included weight as per the licence	Head of Clinical Policy Team (reviewed by Specialised Commissioning Pharmacy Lead)	26/11/2020
and over	and/or 30kg or more	Amended first sentence of the	Included weight as per the licence	Head of Clinical Policy Team (reviewed by	26/11/2020

		Criteria for Commissioning		Specialised Commissioning Pharmacy Lead)	
Recommended dosing for delamanid in children (age 3+ years), by weight (taken from: The Sentinel Project, 2019): • 24-34kg: 50 mg twice daily • >34kg: 100 mg twice daily	Recommended dosing for delamanid in children (age 3+ years and/or 30kg or more), by weight: • 30-49kg: 50 mg twice daily • 50kg or above: 100 mg twice daily	Amended the dosing for delamanid in children in the Criteria for Commissioning Section		Head of Clinical Policy Team (reviewed by Specialised Commissioning Pharmacy Lead)	26/11/2020