Clinical Commissioning Policy
Nebulised liposomal amikacin for the treatment of non-tuberculous mycobacterial pulmonary disease caused by mycobacterium avium complex refractory to current treatment options (adults and post pubescent children) (2111) [221007P]

Publication date: October 2022 version number: v1.0

Commissioning position

Summary

Nebulised liposomal amikacin for the treatment of non-tuberculous mycobacterial pulmonary disease (NTMPD) caused by mycobacterium avium complex (MAC) refractory to current treatment options within the criteria set out in this document.

The policy is restricted to adults and post pubescent children based on the Summary of Product Characteristics (SmPC) and the commissioning medicine in children within specialised services decision (NHS England, March 2017)

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.

Executive summary

Plain language summary

Mycobacteria are microorganisms that can cause problems in the lungs. This policy refers to non-tuberculous mycobacteria (NTM) of the MAC that cause lung infections in adults and post-pubescent children that do not respond to current treatments. The policy does not include patients with an inherited lung condition called cystic fibrosis.

Patients who are diagnosed with NTM MAC lung infections are treated with a combination of antibiotics that include rifampicin, ethambutol and a macrolide. Depending on how severe the disease is, this treatment is performed intermittently three times a week (in less severe cases) or daily (for severe cases) and is given by mouth.

Forty percent of patients receiving these current treatments fail to respond and the NTM MAC microorganisms are still able to be detected in the fluids produced from their lungs. There are limited treatment options for these patients with NTMPD due to MAC.

This new policy proposes the use of an aminoglycoside called amikacin to be given through a device producing a fine spray of the drug to be inhaled (nebulised amikacin). This delivery through inhalation minimises damage to the kidneys and ears (M Shirley 2019).

What we have decided

NHS England has carefully reviewed the evidence to treat adults and post pubescent patients with NTMPD caused by MAC, without cystic fibrosis, that is refractory to current treatment options with nebulised liposomal amikacin. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This policy covers the use of nebulised liposomal amikacin for the treatment of adults and post pubescent patients with NTMPD caused by MAC, who do not have cystic fibrosis, that is refractory to the current Guidance Based Treatment (GBT). The following guideline details the criteria required for the use of treatments prior to nebulised liposomal amikacin:

- BTS 2017, Guideline for the Management of Non-Tuberculous Mycobacterial Pulmonary disease: https://www.brit-thoracic.org.uk/document-library/guidelines/ntm/bts-guideline-for-the-management-of-non-tuberculous-mycobacterial-pulmonary-disease/
- ATS/ERS/ESCMID/IDSA Clinical Practice Guideline 2020, Treatment of Nontuberculous Mycobacterial Pulmonary Disease (Daley et al 2020)
- NHS England 2017, Commissioning Medicines for Children in Specialised Services March 2017: https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf

Committee discussion

See the committee papers (link) for full details of the evidence.

The condition

The term NTM refers to the mycobacteria other than M. Tuberculosis and M. Leprae variants. These microorganisms are found worldwide in soil and water. They are resistant to extremes of heat, pH, disinfectants and antibiotics (Falkinham JO et al 2013). There are more than 180 species identified, but only a small number of them has been proven to cause disease in humans (JP Euzeby 1997).

The most common species identified worldwide is MAC, which includes Mycobacterium Avium, Mycobacterium Intracellulare and Mycobacterium Chimaera. Reports suggest that MAC comprises 34% to 61% of NTM worldwide (Zweijpfenning SMH et al 2018).

Although other systems can be affected, pulmonary disease is the most prominent. Patients with chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease (ILD) seem to be more sensitive to NTM MAC infections, affecting their quality of life. Around 50% of NTMPD is caused by MAC (Van Ingen et al. 2017).

The presenting symptoms of NTMPD are non-specific and it may not be possible to separate them from those caused by underlying respiratory disease (Cowman et al 2018). However, the radiological presentation is more suggestive, typically falling into two patterns: bronchiectasis with nodules (“nodular bronchiectatic” disease), or cavitation with fibrosis (“fibrocavitary” disease). Chronic productive cough, shortness of breath, haemoptysis, malaise, chest pain, fevers, night sweats, loss of appetite and loss of weight are the most commonly reported symptoms.

The disease can present heterogeneously. The features of non-severe NTMPD are acid-fast bacilli (AFB) smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness. In severe NTMPD, there are AFB smear-positive respiratory tract samples, radiological evidence of lung

cavitation/severe infection, or severe symptoms/signs of systemic illness (Haworth et al BTS Guidelines 2017).

In a systematic review of the literature by Diel et al 2018 it was found that the five-year all-cause mortality exceeded 25% in patients with NTMPD due to MAC.

Current treatments

Currently, a few patients with NTMPD MAC do not require treatment. Unlike tuberculosis (TB), diagnosis of the disease does not necessitate treatment (Cowman et al 2019).

For patients that require treatment, the current UK GBT has been set by the British Thoracic Society and includes rifampicin, ethambutol, azithromycin or clarithromycin (Haworth et al BTS Guidelines 2017). Currently, if there is culture conversion the treatment continues for at least 12 months.

Proposed treatments

The policy aims to offer a treatment option to the cases of patients with NTMPD caused by MAC who do not have cystic fibrosis and are refractory to the current GBT. It involves the use of nebulised liposomal amikacin in addition to the current oral GBT. Amikacin (an aminoglycoside antimicrobial) binds to a specific receptor protein on the 30S ribosome subunit of bacteria and interferes with an initiation complex between messenger RNA and the 30S subunit resulting in inhibition of protein synthesis (SMPC). Liposomal amikacin is administered by oral inhalation via a nebuliser, within marketing authorisation arrangements, and is licenced in the UK for adults.

Epidemiology and needs assessment

The UK prevalence of the diagnosed NTMPD in 2016 was 5.1 per 100,000 (Doyle et al 2020). International prevalence rates suggest NTM cases are increasing (Griffith et al 2018).

MAC is the most common species causing about 50% of the NTMPD. Around 60% of patients with NTMPD caused by MAC receive treatment with GBT and around 40% of these will be refractory to GBT (Kwak et al. 2017). Thus, the presumed population that could benefit from this treatment in England (total current population 56,500,000) is approximately 346 patients annually.

Evidence summary

An independent evidence review was conducted for the use of nebulised liposomal amikacin for the treatment of patients with NTMPD caused by MAC with refractory disease to the current treatment options who do not have cystic fibrosis.

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

The evidence review which informs this commissioning position can be accessed here.

Implementation Criteria

NHS England will routinely commission nebulised liposomal amikacin in combination with GBT in accordance with the patient pathway for patients meeting the following inclusion criteria:

Inclusion criteria

Adults and post pubescent children meeting all the following inclusion criteria:

- diagnosis of NTMPD caused by MAC using sputum, induced sputum, bronchial washings, bronchoalveolar lavage or transbronchial biopsy samples (if sputum cultures are negative but clinical suspicion of NTM infection is high, CT-directed bronchial

washings to obtain targeted samples can be used) (Haworth et al BTS Guidelines 2017) that:

- have been treated with GBT for at least 6 months AND
- have failed to show sputum culture conversion.

Exclusion criteria

- Individuals with cystic fibrosis.
- Treatment should not be initiated or should be temporarily interrupted in patients with any of the following:
  - hypersensitivity reaction to aminoglycosides
  - hypersensitivity to soya
  - co-administration with any aminoglycoside administered via any route of administration
  - severe renal impairment.

Starting criteria

Nebulised liposomal amikacin should be initiated and managed by physicians with significant experience in the treatment of refractory NTMPD due to MAC. The prescribing organisation is responsible for the ongoing prescribing of the treatment and the facilitation of homecare arrangements.

Stopping criteria

A decision to stop using nebulised liposomal amikacin should be made by the clinician with significant experience in managing refractory NTMPD due to MAC, along with the patient and carers (if applicable) using the following criteria:

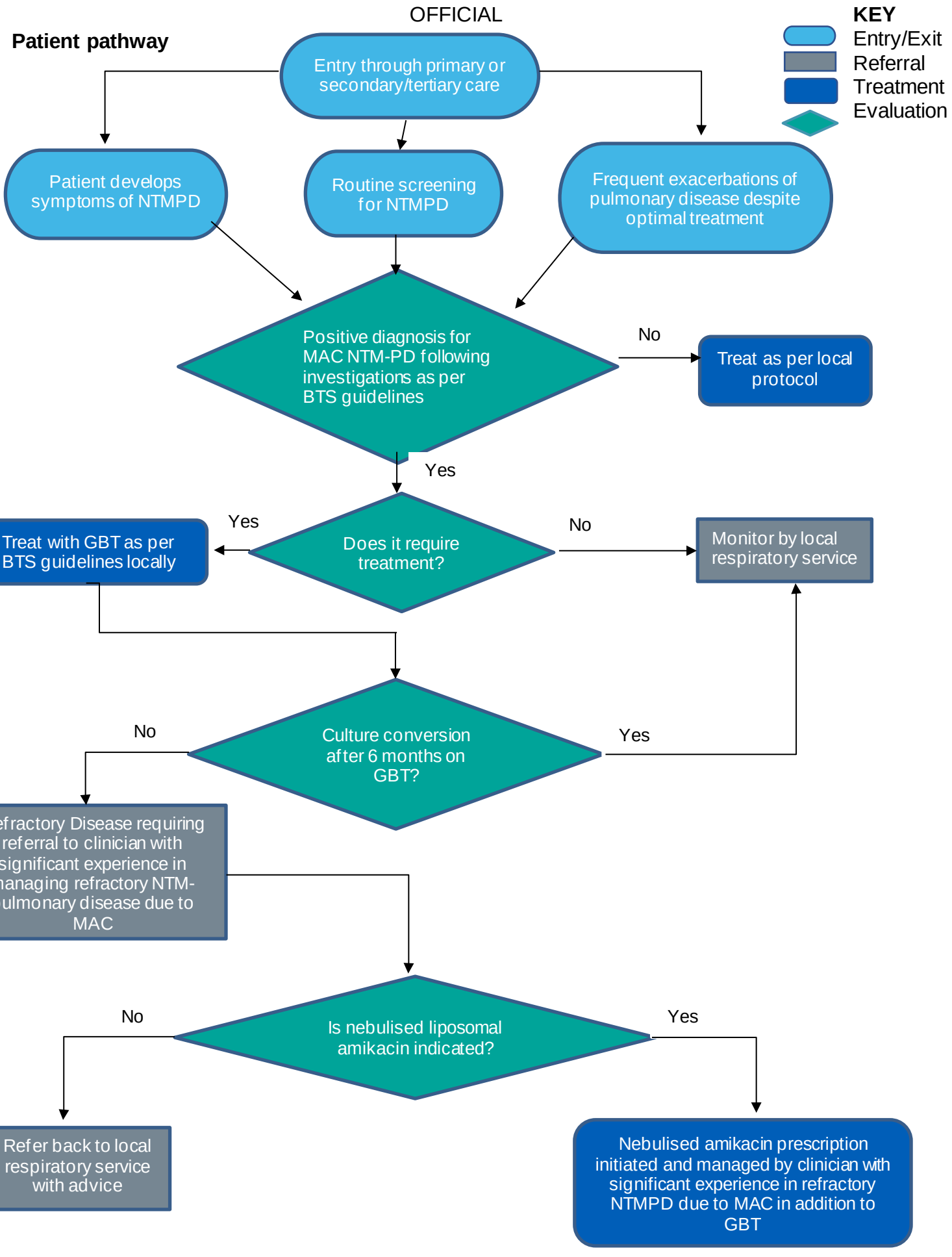
- No culture conversion or worsening symptoms, by 6 months
- Adverse events where harm exceeds benefit at any time during treatment.

Dose

The recommended dosage is 1 vial administered once daily, by oral inhalation. Each vial contains amikacin sulphate equivalent to 590 mg amikacin in a liposomal formulation. The mean delivered dose per vial is approximately 312 mg of amikacin (NICE ES36 2021).

Treatment with nebulised liposomal amikacin, as part of a combination antimicrobial regimen, should be continued for 12 months after sputum culture conversion. Treatment should not continue beyond a maximum of 6 months if sputum culture conversion has not been confirmed by then. The maximum duration of treatment should not exceed 18 months.

Patient pathway



The diagnostic process for NTMPD MAC can be triggered in primary, secondary, or tertiary care, due to symptoms typical of the disease, due to routine screening for NTMPD MAC or following frequent exacerbations of chronic pulmonary conditions despite optimal treatment.

The respiratory team decides if treatment is needed after a diagnosis of NTMPD MAC is made, according to BTS guidelines (Haworth et al BTS Guidelines 2017). If treatment is required, GBT is started. If the disease responds to GBT, the treatment continues within the local respiratory service.

If the disease is refractory to GBT after at least 6 months on treatment, the patient is referred to a clinician with significant experience in managing refractory NTMPD due to MAC. Following assessment from the clinician nebulised liposomal amikacin can be initiated in addition to the current oral GBT. The prescribing organisation is responsible for the ongoing prescribing and the provision of the treatment through homecare arrangements.

The prescribing team is also responsible for assisting patient groups that might require extra support in managing their treatment (patients with learning difficulties, mental health problems, homeless, patients under the criminal justice system, patients with addictions and substance misuse, patients with poor literacy and/or health literacy, patients living in rural or remote areas, refugees, asylum seekers).

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 prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Nebulised liposomal amikacin for the treatment of adults and post pubescent patients with NTMPD caused by MAC refractory to the current GBT who do not have cystic fibrosis will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements.

Audit requirements

The prescribing organisation carry the responsibility of keeping an electronic record of the patients involved in the treatment with nebulised liposomal amikacin, reporting side effects and auditing the outcomes of the treatment.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

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.

Definitions

Guidance Based Therapy (GBT)	Therapy approved by the British Thoracic Society (Haworth et al BTS Guidelines 2017)
Refractory disease	Disease that has not responded to GBT after 6 months of treatment
Sputum Culture Conversion	No isolation(s) of MAC in the sputum culture(s) in a patient with previously positive MAC sputum culture

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