CLINICAL PRIORITIES ADVISORY GROUP
18 07 2022

Agenda Item No	5.1
National Programme	Internal Medicine
Clinical Reference Group	A01 Specialised Respiratory
URN	2111

Title
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)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
For routine commissioning. Mycobacteria are microorganisms that can cause problems in the lungs. This policy proposition 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 proposition 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 proposition 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).

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Outcome 1 **Culture conversion** **Certainty of evidence:** Very low to high	Culture conversion means that the patient no longer tests positive for the MAC organisms in their sputum. This is a critical marker of treatment success to patients and clinicians as it indicates whether treatment should continue and when treatment can end. Culture conversion should be attained by 6 months of treatment with nebulised liposomal amikacin plus GBT.

	Two randomised trials: one phase 2 double blind RCT (Olivier et al 2017, n = 89) and one open-label phase 3 controlled study (CONVERT study; Griffith et al 2018, n = 336) provided evidence relating to the effectiveness of LAI in converting culture positive NTM PD caused by MAC, after 3 and 6 months of treatment respectively. Evidence for the culture conversion beyond six months and for sustainability and durability of conversion was provided by two open label follow-up studies of the patients recruited to the CONVERT study. Griffith et al 2021 (n = 75) evaluated the sustainability and durability among those participants who converted (converters) in the first 6 months and remained negative at 8 months evaluation following the CONVERT study. The study by Winthrop et al 2021 (n = 163) evaluated the efficacy and safety of open label LAI treatment in both LAI-naïve or prior-LAI patients who failed to convert (non-converters) or relapsed during the 6-month trial phase of the CONVERT study. **At 84 days** • Olivier et al 2017 (n = 89) reported the change in semi-quantitative mycobacterial culture results from baseline to day 84 for LAI vs placebo: 2.0 SD vs 1.5 SD, p= 0.072. NS **(MODERATE)** • Olivier et al 2017 reported culture conversion rates of LAI 32% (14/44) in patients treated with LAI vs 9% (4/45) in patients treated with placebo, p = 0.006. (**MODERATE)** • Olivier et al 2017 reported a shorter time to first negative sputum culture with LAI vs placebo: HR 5.68, 95% CI 1.25 to 25.79, p = 0.0129. **(MODERATE)** **At 168 days** • After an open-label follow-up phase, Olivier et al 2017 reported conversion rates of LAI 31.4% [11/35] vs placebo 9.3% (4/43). At 28-days after end of study follow-up, conversion rates were LAI 31.4% (11/35) vs placebo 7.0% (3/43). **(LOW)** **At 6 months** • Griffith et al 2018 reported culture conversion rates of 29% (65/224) in patients treated with LAI + GBT vs GBT alone 8.9% (10/112); adjusted odds ratio 4.22, 95% CI 2.08 to 8.57, p<0.001. HR 3.90, 95% CI 2.00 to 7.60. **(HIGH)** • Winthrop et al 2021 (n=163) in an open-label parallel group study evaluated the conversion rates amongst

	patients who did not convert at the end of the 6-month open label randomised phase of the CONVERT study. At 6 months, the authors reported a cumulative sputum culture conversion of 26.7% (24/90) in LAI-naïve patients, increasing to 30/90 (33.3%) by Month 12. The study also reported cumulative culture conversion of 7/73 (9.6%) in prior-LAI patients at 6 months increasing to 10/73 (13.7%) at 12 months. **(VERY LOW)** **At 12 months** • Griffith et al 2021 reported sustained conversion rates at 12 months: LAI + GBT 41/224 (18.3%) vs GBT alone 3/112 (2.7%), p<0.0001 (ITT analysis), and LAI + GBT 41/65 (63.1%) vs GBT alone 3/10 (30.0%), p=0.0644 (converter analysis). **(MODERATE)** **At end of treatment (up to 16 months)** • Griffith et al 2021 reported sustained conversion at the end of treatment of LAI + GBT 52/224 (23.2%) vs GBT alone 3/112 (2.7%), p< 0.0001; LAI + GBT 52/65 (80.0%) vs GBT alone 3/10 (30.0%), p= 0.0014 (converter analysis). **(MODERATE)** **At 3 months from the end of treatment** • Griffith et al 2021 reported durable conversion rates at 3-month follow-up from end of treatment of LAI + GBT 36/224 (16.1%) vs GBT alone 0/112, p<0.0001 (ITT analysis); LAI + GBT 36/65 (55.4%) vs GBT alone 0/10, p=0.0017 (converter analysis). **(LOW)** **At 12 months after treatment** • Griffith et al 2021 reported negative culture results 12 months after treatment rates of LAI + GBT 30 (13.4%) vs GBT alone 0, p<0.0001 (ITT analysis); LAI + GBT 30/65 (46.2%) vs GBT alone 0/10, p<0.0001 (converter analysis). **(LOW)** • Conversion rates regardless of treatment duration were LAI + GBT 41/224 (18.3%) vs GBT alone 0/112, p<0.0001 (ITT analysis); LAI + GBT 41/65 (63.1%) vs GBT alone 0/10, p=0.0002 (converter analysis). **(LOW)** **These studies provide very low to high certainty evidence that LAI + GBT produces significantly higher culture conversion rates compared to placebo or GBT alone at 84 days to 6 months follow-up. They also provide low to moderate certainty evidence that the culture conversion is**

	sustained at 12 months of treatment and persists at 3 months follow-up following discontinuation of treatment.
Outcome 2 **Health-related Quality of Life (HrQOL)** **Certainty of evidence:** Low to moderate	Health-related quality of life can be measured by respiratory-specific subjective scales such as the St George's Respiratory Questionnaire (SGRQ). Quality of life is a critical outcome for patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived wellbeing. A difference of 4 or more points is considered an MCID for the St George's Respiratory Questionnaire. Two RCTs (Olivier et al 2017, Griffith et al 2018) evaluated the effect of LAI on HrQOL at 84 days to 6 months. • At 84 days, one double blind placebo-controlled RCT (Olivier et al 2017) reported a change from baseline in SGRQ, QOL, QOL bronchiectasis, and NTM module scores between non-CF patients treated with LAI (n = 36) -7.935 (SD 14.1998) vs placebo (n = 36) -2.829 (13.6733), p= 0.2039. **(MODERATE)** • At 6 months, one open-label RCT (Griffith et al 2018) reported least squares mean (SE) changes from baseline in SGRQ score: LAI + GBT vs GBT alone: 4.2 (2.0) vs 0.4 (2.2), MD [SE] 3.8 [1.6], 95% CI 0.67 to 6.94. **(LOW)** **These studies provide low to moderate certainty evidence that LAI + GBT produced numerical improvements in SGRQ score changes from baseline at 84 days and at 6 months. These were not statistically significant.**
Outcome 3 **Mortality** **Certainty of evidence:** n/a	This outcome is critical to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Mortality reported within any timeframe is relevant. **No evidence was identified for mortality.**
Important outcomes	
Outcome 4 **6-minute walk test** **Certainty of evidence:** Very low to moderate	The 6-minute walk test (6MWT) is an important outcome for patients as it is an objective marker of their exercise capacity. Changes in the 6-minute walk test would be expected to be seen at 4 to 6 months and may be monitored up to the end of treatment (no longer than 18 months from initiation). There are no recorded MCIDs. Two RCTs (Olivier et al 2017 and Griffith et al 2018) evaluated the effect of LAI on the 6MWT at 84 days to 6 months • One double-blind RCT (Olivier et al 2017) reported a mean (SD) distance walked at 84 days, LAI +20.6 (SD,

	62.4) meters vs placebo -25.0 (100.2) meters, p= 0.017. **(MODERATE)** • At 168 days (end of open-label phase), Olivier et al 2017 reported a change in mean (SD) 6MWTs of prior-LAI (n = 35), +142.4 (105.9) meters vs prior-placebo (n = 43), -228.4 (88.1) meters, MD 70.8 metres, p= 0.012. **(VERY LOW)** • At 6 months, one open label RCT (Griffith et al 2018) reported a mean 6-minute walk test Change in 6MWT distance from baseline to Month 6 of LAI + GBT (n = 223) -1.5 (-23.6 to 20.6) vs GBT alone (n = 112) 1.5 (-22.2 to 25.3). Least squares MD [SE] -3.0 [9.0], 95% CI -20.64 to 14.65, p= 0.74. **(LOW)** • An open label follow-up to the CONVERT study, Griffith et al 2021 reported mean changes in 6MWT from baseline in 75 patients who converted during the double-blind phase of the CONVERT study. At 3 months follow-up after 12 months of treatment in total, the mean change in 6MWT from baseline was: LAI + GBT 83.4 (SD 20.9 ± 83.4) m, p= 0.096; GBT only group was not calculable **(LOW)** **These studies provide very low to moderate certainty evidence on the effectiveness of adding LAI to GBT in terms of 6MWT improvements. However, the data are conflicting. While the double-blind study (Olivier et al 2017) reports a significant improvement in 6MWT at 84 days which is also observed at 168 days follow-up, in the study by Griffith et al 2018. In the follow-up study by Griffith et al 2021, there was no significant difference between treatment arms in the change from baseline in the 6MWT distance at 6 months and no significant improvement in 6MWT at 3 months follow-up after 12 months of LAI treatment.**
Outcome 5 **Lung function** **Certainty of evidence:** Moderate	Lung function is usually measured by spirometry and gives an objective measure of how well the lungs are working. Measures would include, but not be limited to forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). This is an important outcome for patients as it is an objective marker of the change in their lung function. Changes would be expected after 4 to 6 months of treatment. There are no recorded MCIDs. One RCT (Olivier et al 2017) reported the increases in FEV1 per cent predicted in both arms of the study: • At 84 days, increases in FEV1 were: LAI 0.32 ± 0.5% vs placebo 0.16 ± 6.0%. (It was not reported whether these

	were mean or median differences; no p-value was reported. **(MODERATE)** **This study provides moderate certainty evidence for a small, clinically insignificant increase in FEV1 with both LAI and placebo at 84 days of treatment.**
Outcome 6 **Adherence to treatment** **Certainty of evidence:** Low	Adherence to treatment is important to patients because it is vital to the function of the medication that it is taken regularly as prescribed in order to gain the maximum effect, improve outcomes, and prevent complications. It is not known what the lowest level of adherence is needed for treatment success. • One open-label follow-up study (Griffith et al 2021) reported low certainty evidence for high adherence rate (81.5%) in adults treated with LAI + GBT. Comparative adherence rates with GBT alone were not reported. No measures of statistical significance were reported. **(LOW)** **This study provided low certainty evidence for high adherence rates in adults treated with LAI + GBT. Comparative adherence rates with GBT alone were not reported.**
Outcome 7 **Radiographic changes** **Certainty of evidence:** n/a	Changes to the appearance of x-rays and computerised tomography scans are important to patients as they are used to help determine treatment success and requirement for further treatment. Changes would be expected after 4 to 6 months of treatment. **No evidence was identified for radiographic changes.**
Safety	
Outcome 1 **Safety** **Certainty of evidence:** Very low to high	The benefits of LAI treatment may be countered by the presence of serious treatment-emergent adverse events (grade 3, 4 or 5) including (but not limited to) pneumonia, exacerbation of underlying airways conditions, renal toxicity, haemoptysis, and ototoxicity. Treatment-emergent adverse events could also lead to treatment discontinuation, thereby limiting patients' ability to derive benefit from treatment. Ototoxic and nephrotoxic effects are common treatment-limiting adverse effects to aminoglycoside antibiotics like amikacin. The liposomal amikacin formulation LAI was designed to facilitate targeted and localized drug delivery to the lungs while minimizing systemic exposure. Significant ototoxicity or nephrotoxicity with LAI treatment will therefore negate the theoretical benefits of administering amikacin as a nebulised liposome enclosed product. The safety of LAI treatment was evaluated in two randomised studies (Olivier et al 2017 and Griffith et al 2018 (CONVERT study)). Longer-term safety was evaluated in two open follow-up studies to the CONVERT study; one in patients who converted after the 6-month trial period (Griffith et al 2021) and another in

	patients who did not convert after the trial period (Winthrop et al 2021). **At 84 days** *Serious adverse effects* • In the double-blind placebo-controlled RCT (Olivier et al 2017), the overall incidence of serious adverse events was higher in the LAI group than in the placebo group (18.2% vs 8.9%). **(MODERATE)** *Treatment-emergent adverse events (TEAE) included:* • Grade 3: LAI 4/44 (9.1%) vs placebo 5/45 (11.1%) **(LOW)** • Grade 4: LAI 0 (0%) vs placebo 0 (0%) **(VERY LOW)** • Grade 5: LAI 1/44 (2.3%) vs placebo 0/45 (0%) **(LOW)** *TEAE leading to discontinuation* • In the double-blind phase of the RCT by Olivier et al 2017 17/44 (15.9%) patients in the LAI group and none in the placebo group discontinued the study drug because of TEAE. **(LOW)** **At 168 days** *Serious adverse effects* • During the open-label phase of the study by Olivier et al 2017, the incidence rates of serious adverse events were prior-LAI 14.3% vs prior-placebo 11.6%. **(VERY LOW)** *TEAE leading to discontinuation* • occurred in fewer patients initially treated with LAI compared to those who received placebo during the double-blind phase of the RCT by Olivier et al 2017: LAI 6 (17.1%) vs placebo 12 (27.9%) **(VERY LOW)** *Renal adverse effects* • Events related to nephrotoxicity were infrequent in both arms. **(LOW)** **At 6 months** *Serious adverse effects* • In the open-label RCT (Griffith et al 2018), serious TEAEs were reported in both groups: LAI+GBT 45**/**223 (20.2%) vs GBT alone 20/112 (17.9%) **(HIGH***)* *TEAEs leading to death*

	• In the open-label RCT (Griffith et al 2018), TEAEs leading to death were reported in both groups: LAI+GBT 6/223 (2.7%) patients vs GBT alone 5/112 (4.5%). **(HIGH)** *Audiologic* TEAEs • Audiologic TEAEs were reported in both arms of the open-label RCT study by Griffiths et al 2018 including tinnitus: LAI+GBT 17/223 (7.6%) vs GBT alone 1/112 GBT (0.9%) **(HIGH)** **At up to 16 months** Griffiths et al 2021 reported adverse outcomes for patients who were culture-negative at 8 months who were followed up for up to 16 months (end of treatment – EOT). • Any serious TEAE: LAI + GBT 6/65 (9.2%) vs GBT alone 6/10 (60.0%) **(LOW)** • COPD exacerbation: LAI + GBT 1/65 (1.5%) vs GBT alone 2 (20.0%) **(LOW)** • Drug hypersensitivity: LAI + GBT 1/65 (1.5) vs GBT alone 0 **(VERY LOW)** • Infective exacerbation of bronchiectasis: LAI + GBT 1 (1.5%) vs GBT alone 1 (10.0%) **(LOW)** • Infective exacerbation of COPD: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Lung adenocarcinoma: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Lung infection pseudomonal: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Pneumatosis intestinalis: LAI + GBT 1 (1.5) vs GBT alone 0 (**VERY LOW)** • Pneumonia: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Pneumothorax: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** **These studies provide very low to high certainly evidence on the safety of LAI+GBT compared with GBT alone. TEAEs including serious effects including those leading to discontinuation were more common in the LAI group and were mostly respiratory effects. Renal effects are minimal. The most common audiovestibular effects associated with LAI were tinnitus and dizziness.**

In the Population what is the cost effectiveness of the Intervention compared with Comparator?

Outcome	Evidence statement

Cost effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with nebulised liposomal amikacin with GBT compared with treatment with GBT alone.

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have moderate to severe problems in walking about.
- **ability to provide self-care:** Patients have moderate to severe problems in washing or dressing.
- **undertaking usual activities:** Patients have moderate to severe problems in doing their usual activities and in some cases are unable to do their daily activities
- **experience of pain/discomfort:** Patients have moderate to severe discomfort from the respiratory system
- **experience of anxiety/depression:** Patients are moderately to severely anxious or depressed

Further details of impact upon patients:

Patients suffering from Non-Tuberculous Mycobacterial Pulmonary Disease (NTMPD) caused by the Mycobacterium Avium Complex (MAC) experience symptoms from their respiratory system, mainly, chronic productive cough shortness of breath, haemoptysis. Other systemic symptoms include malaise, chest pain, fevers, night sweats, loss of appetite and loss of weight. Those symptoms seem to be even more prominent in patients with pre-existing lung disease.

Currently, NT- MAC patients are receiving a standard treatment that, unfortunately, fails to provide positive outcomes in 40% of the cases. Nebulised liposomal amikacin aims to provide a further level of care when current treatment options have failed or not tolerated/contraindicated.

Due to the effects of the disease and the symptoms experienced, most patients find it difficult to mobilise and undertake normal daily activities (shopping, looking after family members, housework etc). Although in many cases they can self-care, when the disease progresses to severe, that ability becomes limited (requiring help from carers). The increasing shortness of breath can cause significant discomfort. The PWG acknowledged the significant impact on patients' life as described by the patients' representative.

The patients are attending many hospital appointments and receive regular medical treatment. The standard treatment consists of a regimen of multiple antibiotics for over a year and leads to significant intolerances and side effects. In cases of deterioration, the patients are admitted in the hospital. Some patients require to have a peripherally inserted central catheter (PICC). Those elements have an effect on patients' social life and mental health. Furthermore, constant cough can lead to anxiety being around others and sleep deprivation, that deteriorates the mental health problems.

The current literature suggests that patients with this disease have a five-year all-cause mortality that is exceeding 25%.

Further details of impact upon carers:

Family members have to commit a lot of their personal time in order to care for patients with NTMPD. In many cases they had to leave their employment and put their personal life on hold. The impact on family life can only be imagined, especially when deteriorations in health mean repeated visits in the hospital.

The psychological burden of the disease to patients, carers and the wider family increases as the disease progresses and there is need for more support around care and housework.

The constant cough can cause sleep deprivation to the carers as well.

In addition, worsening health can lead to patients and carers not being able to fulfil their family duties leading to financial, physical and emotional strains

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
The policy proposition supports the use of nebulised liposomal amikacin, in combination with guideline-based therapy (GBT), for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis, in line with its marketing authorisation. It is excluded from tariff. Post pubescent children will be able to access liposomal amikacin under the Medicines for Children Policy.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine PoC on the 7th June 2022.