Cost-effectiveness of inhaled liposomal amikacin (Arikayce®) for the treatment of non-tuberculosis mycobacterial (NTM) lung infections due to Mycobacterium avium Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis (CF)

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of inhaled liposomal amikacin (Arikayce®). Following assessment of the Applicant's submission, the NCPE recommends that inhaled liposomal amikacin (Arikayce®) be considered for reimbursement if cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an evaluation of the Applicant's (Insmed Limited) Health Technology Assessment dossier on inhaled liposomal amikacin (Arikayce®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **December 2022**

Summary

In March 2022, Insmed Limited submitted a dossier of clinical, safety and economic evidence on inhaled liposomal amikacin (Arikayce®) for the treatment of non-tuberculosis mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis (CF). Insmed Limited are seeking reimbursement through the High Tech Drug Arrangement.

Where indicated, systemic treatment usually involves a combination of antibiotics (also referred to as guideline-based therapy [GBT]) taken over 12 months or more. International guidelines recommend that GBT comprises three antibiotics; such triplet regimens are the standard of care (SOC) in Ireland. One aim of treatment is to achieve sputum culture conversion (i.e. from MAC positive to MAC negative sputum cultures). In clinical practice, sputum culture conversion is understood to be defined as three consecutive MAC negative sputum cultures, with the date of conversion being the date of the first MAC negative sputum culture. A further aim, of treatment, is to achieve a durable culture conversion.

Amikacin is an aminoglycoside. It inhibits protein synthesis by binding to a 30S subunit of bacterial ribosomes and interfering with an initiation complex between mRNA (messenger RNA) and the 30S subunit. Arikayce® (a novel liposomal formulation of amikacin) is administered via oral inhalation with the LAMIRA® Nebuliser System at a dose of 590mg once daily in combination with GBT. If sputum culture conversion does not occur after a maximum of six months of treatment, inhaled liposomal amikacin should be discontinued. Clinical opinion, to the Review Group, indicates that GBT would also be discontinued here. Where sputum culture conversion does occur, it is recommended that treatment continues for 12 months after. Maximum duration of treatment overall should not exceed 18 months as per the Summary of Product Characteristics (SmPC).

1. **Comparative effectiveness of inhaled liposomal amikacin plus GBT versus GBT only**

Clinical evidence, for the regulatory approval of inhaled liposomal amikacin, is from the CONVERT trial and an extension study.

CONVERT was a phase III, open-label, randomised active-controlled trial which compared inhaled liposomal amikacin plus GBT (n=224) versus GBT only (n=112) in adult patients with

refractory MAC lung disease. Eligible patients had not achieved sputum culture conversion whilst on at least six months treatment with GBT prior to trial entry.

In the trial, patients who achieved sputum culture conversion by month six post commencement of study treatment then continued therapy for an additional 12 months after achieving sputum culture conversion. Those who did not achieve sputum culture conversion by month six discontinued the study. Treatment with inhaled liposomal amikacin plus GBT resulted in a statistically significantly greater rate of sputum culture conversion at six months (29%) compared with GBT only (8.9%) (adjusted odds ratio 4.22; 95% confidence interval 2.08 to 8.57; $p<0.0001$). In addition, the rate of durable culture conversion, at three months after completion of treatment, was greater in the inhaled liposomal amikacin plus GBT arm (16.1%) compared with the GBT only arm (0%) ($p<0.0001$).

In an open-label extension study, the primary objective was to assess the safety of inhaled liposomal amikacin plus GBT in patients enrolled in the CONVERT trial and who had completed the month six and eight visits but failed to achieve confirmed sputum culture conversion or had experienced a relapse or recurrence.

The Review Group highlight a number of key limitations in the CONVERT clinical evidence:

- CONVERT was an open label trial and therefore bias may be introduced, particularly for patient-reported outcomes such as adverse events and health-related quality of life.
- There were high patient withdrawal rates in the trial (19.6% in inhaled liposomal amikacin plus GBT arm vs 8.9% in GBT only arm) at the six-month sputum culture conversion analysis, increasing to 27.2% and 12.5% respectively at the final analysis).
- The median duration of GBT treatment prior to trial enrolment was 3.9 years. This is not reflective of Irish clinical practice where GBT is generally discontinued if sputum culture conversion is not achieved after six months of treatment.
- At baseline, treatment consisted of only two antibiotics in 17.5% of patients in the inhaled liposomal amikacin plus GBT arm, and in 12.5% of patients in the GBT only arm. Patients remained on their respective antibiotic regimens on trial entry. Clinical

opinion indicated that, in the Irish setting, only triplet regimens are used, in line with international clinical guidelines.

2. Safety of inhaled liposomal amikacin

The safety profile of inhaled amikacin liposomal was assessed in the CONVERT pivotal trial and extension study. In both studies, most patients experienced at least one treatment emergent adverse event (TEAE). In the CONVERT trial, 98.2% (inhaled liposomal amikacin plus GBT), and 91.1% (GBT only) experienced a TEAE, and 96.9% experienced a TEAE in the extension study. The most commonly reported respiratory adverse events were dysphonia (42.6%), cough (30.9%), dyspnoea (14.4%), haemoptysis (10.9%), oropharyngeal pain (9.2%), and bronchospasm (2.2%). Most common serious adverse events included chronic obstructive pulmonary disorder (1.5%), haemoptysis (1.2%), and infective exacerbation of bronchiectasis (1.0%). The SmPC carries special warnings regarding the risks of developing allergic alveolitis; bronchospasm; exacerbation of underlying pulmonary disease; ototoxicity; nephrotoxicity and neuromuscular blockade.

3. Cost effectiveness of inhaled liposomal amikacin

Methods

The cost effectiveness of inhaled liposomal amikacin plus GBT versus GBT only was investigated in an individual-patient microsimulation, health-state transition model (Excel®). To estimate costs and outcomes, individual patient 'profiles' were drawn at random (based upon the CONVERT trial population), and their pathway through the model was simulated multiple times under both treatments. Population-level results were then estimated by calculating mean costs and QALYs.

The model consisted of five mutually exclusive health states: 'MAC positive,' 'MAC negative,' 'Microbiological cure', 'Surgery' and 'death.' All patients entered the model in the MAC positive state, and could move to the MAC negative state during the first six months of treatment. Patients who failed to achieve sputum culture conversion by month six remained in the MAC positive state (and on treatment with GBT for life). Those in the MAC negative state remained at risk of recurrence or reinfection (i.e. transition back to MAC positive state). After 12 months in the MAC negative state, patients automatically transitioned to the

microbiological cure state. In the microbiological cure state, treatment was stopped, though relapse/reinfection remained a possibility. Upon recurrence/reinfection all patients were treated with GBT, i.e., no retreatment with inhaled liposomal amikacin was assumed. Death was possible from any health state, with increased risk of mortality in the MAC positive and MAC negative states compared with the microbiological cure state. Surgery was not included as a treatment option in the base case.

Treatment effectiveness in the model was captured via improved survival arising from a greater probability of transitioning to MAC negative and onwards to microbiological cure, and improved quality of life associated with these health states. The main treatment effect in the model was sputum culture conversion, i.e. transition from MAC positive to MAC negative status. Probabilities of sputum culture conversion were estimated from time-to-sputum culture conversion data from the CONVERT trial using parametric survival regression models. A secondary treatment effect was the reduced risk of recurrence/reinfection from MAC negative in the inhaled liposomal amikacin plus GBT arm compared with the GBT only arm (based on analysis of recurrences/reinfections in the CONVERT study). The risk of recurrence/reinfection from microbiological cure was assumed to be equal across treatment arms.

The model included drug and administration costs, as well as additional costs related to management of adverse events, MAC lung disease and related complications. Drug costs were based on modelled outcomes (including early discontinuation, estimated from the CONVERT trial) and associated stopping rules. An adherence rate of 86%, estimated from the inhaled liposomal amikacin plus GBT arm of the CONVERT trial, was applied to both treatment arms in the model. While drug costs were substantially higher in the inhaled liposomal amikacin plus GBT arm this was partially offset by reductions in other MAC lung disease related costs. Treatment-specific utility values, (estimated from CONVERT) were applied in the base case. Utility values were higher in the MAC negative state compared with the MAC positive state, and higher again in the microbiological cure state, as expected. However, the Review Group noted that some utility values appeared to be implausibly high, and considered the Applicant's approach to handling repeated measurements and missing data to have been a possible source of bias in the utility estimates.

The Review Group note that the handling of missing sputum culture data from the CONVERT trial may have resulted in bias in treatment effect estimates due to informative censoring.

Also, there was much uncertainty associated with the long-term recurrence rates, mortality rates, and utility estimates.

Results

In the Applicant's base case, inhaled amikacin liposomal plus GBT was associated with an incremental cost of €59,192 and an incremental QALY of 0.69 versus GBT only, resulting in an incremental cost effectiveness ratio (ICER) of €85,879 per QALY. The probabilities of cost effectiveness at both the €20,000 per QALY and €45,000 per QALY thresholds were 0% and 2% respectively.

The NCPE-adjusted base case comprised a number of changes to the Applicant's base case including:

- Removal of the extrapolation of sputum culture conversion rates from month four (which was the last possible date of sputum culture conversion in CONVERT)
- Removal of the assumption that patients who do not convert (in both arms) would remain on GBT for life (this assumption is not in line with Irish clinical practice).
- The Applicant assumed that recurrence would lead to treatment with GBT in all patients. The NCPE assumed that 50% of patients would be retreated with GBT and 50% would receive no further treatment (with no possibility of transitioning to the MAC negative state).

In the NCPE-adjusted base case, inhaled liposomal amikacin plus GBT was associated with an incremental cost of €61,299 and an incremental QALY of 0.47; ICER of €129,777 per QALY. The probabilities of cost effectiveness at both the €20,000 per QALY and €45,000 per QALY thresholds were 0%.

Table 1 Results of cost-effectiveness analysis under the Applicant and NCPE's adjusted base case assumptions (deterministic)

Treatment	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	Pairwise ICERs (€/QALY)
Applicant Base Case					
Inhaled liposomal amikacin plus GBT	280,071	8.32			
GBT only	220,878	7.63	59,192	0.69	85,879

NCPE Adjusted Base Case					
Inhaled liposomal amikacin plus GBT	234,029	8.15			
GBT only	172,729	7.68	61,299	0.47	129,777

QALY: quality-adjusted life-year**; ICER:** incremental cost effectiveness ratio.
A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations may not be directly replicable. Results are subject to random variation in the simulation process.

Sensitivity analysis

In both the NCPE-adjusted and Applicant's base case, the probabilistic ICERs were similar to the deterministic ICERs. The most influential parameter affecting the ICER was the discount rate for health outcomes. Other influential parameters included recurrence rates, discontinuation rates for inhaled liposomal amikacin, and the magnitude of mortality risk associated with MAC lung disease.

The Review Group highlight, in particular, the following key scenario analyses:

- When it is assumed that treatment effectiveness in the model is based upon confirmed cases of sputum culture conversion from the CONVERT trial alone (i.e. without further assumptions and extrapolations), the ICER increases to €162,422 per QALY.
- When 100% treatment adherence is assumed, the ICER increases to €157,156 per QALY.
- When it is assumed that patients who test positive at month four discontinue treatment immediately, the ICER decreases to €113,590 per QALY.

4. Budget impact of inhaled liposomal amikacin

The price to wholesaler for one pack (28 x 590mg vials) of inhaled liposomal amikacin is €10,570. Assuming an adherence rate of 86% and a mean treatment duration of eight months (from CONVERT), the total drug acquisition cost of inhaled liposomal amikacin plus GBT, per patient, per treatment course is €82,450 (VAT not applicable). If 100% adherence is assumed, the cost, per patient, per treatment course is €95,872 (VAT not applicable). The Applicant estimates that 31 patients in Ireland will be eligible for treatment over five years. The five-year cumulative gross and net budget impacts (assuming 100% adherence) are an estimated €2.7 million and €2.6 million respectively.

5. Patient Submission

No patient organisation submissions were received during the course of this evaluation.

6. Conclusion

The NCPE recommends that inhaled liposomal amikacin, in addition to guideline-based therapy, for the treatment of adult patients with NTM lung infections caused by MAC and who have failed at least six months of guideline-based therapy, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

It is advised that treatment with inhaled liposomal amikacin plus GBT be aligned with antimicrobial stewardship practices.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.