AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Amikacin liposomal (Arikayce®)
590 mg nebuliser dispersion

Reference number: 2140

FULL SUBMISSION

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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AWMSG Secretariat Assessment Report
Amikacin liposomal (Arikayce®) 590 mg nebuliser dispersion

1.0 KEY FACTS

Assessment details	Amikacin liposomal (Arikayce®) for the treatment of nontuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. Arikayce® liposomal should be used in conjunction with other antibacterial agents active against *Mycobacterium avium* Complex lung infections. Arikayce® liposomal consists of amikacin sulfate encapsulated in liposomes. Using the Lamira® Nebulizer System, this technology enables the delivery of liposomal amikacin directly to the lungs.
Current clinical practice	There are currently no other licensed medicines available for the treatment of MAC-NTM lung disease. Welsh clinical experts indicate there are very limited treatment options available. Current clinical practice is based on guideline-based treatment. Treatment guidelines outline a prolonged multi-drug regimen (MDR), typically with a macrolide, ethambutol and a rifamycin, which continues for a minimum of 12 months after sputum culture becomes negative. In severe disease, intravenous amikacin or off-label amikacin solution for injection given by nebulisation can be added to treatment. Arikayce® liposomal is the first antimicrobial to be licensed for the treatment of MAC-NTM lung disease and has recently been included in international treatment guidelines for NTM lung disease. Welsh clinical experts suggest these guidelines are relevant to Welsh practice.
Clinical effectiveness	The pivotal open-label, randomised phase III study compared Arikayce® liposomal plus guideline-based MDR with guideline-based MDR alone in adult patients with treatment refractory MAC-NTM lung disease. The primary endpoint demonstrated a statistically significant proportion of patients receiving Arikayce® liposomal plus guideline-based MDR had improved sputum culture conversion rates (clearing lung infection caused by MAC) at month six compared with guideline-based MDR alone. In addition, three months after stopping treatment, sustained sputum culture conversion (patients who continued to test negative for MAC) was significantly higher in the Arikayce® liposomal plus guideline-based MDR group. Although the effect of Arikayce® liposomal is modest, it is considered to benefit patients who have few treatment options. Arikayce® liposomal can cause significant side effects, particularly during the first months of treatment. Treatment

	should be initiated and managed by physicians experienced in the treatment of NTM lung disease due to *Mycobacterium avium* Complex.
Cost-effectiveness	A cost-utility analysis compares Arikayce® liposomal plus guideline-based MDR (based on a weighted-average of five MDRs) with guideline-based MDR alone for the treatment of adult patients with MAC-NTM lung disease with limited treatment options who do not have cystic fibrosis. The company base case suggests an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] /quality-adjusted life-year (QALY) gained based on the Wales patient access scheme (WPAS) price. The model structure appears robust to sensitivity and scenario analyses provided by the company with ICERs ranging from [commercial in confidence figures removed] and with Arikayce® liposomal plus guideline-based MDR dominated when a time horizon of 6 months was applied. The ICER is most sensitive to Arikayce® liposomal cost and adherence, time horizon and health state utilities.
Budget impact	It is estimated that [commercial in confidence figure removed] patients would receive treatment with Arikayce® liposomal in Wales in Year 1, decreasing to [commercial in confidence figure removed] in subsequent years. Introducing Arikayce® liposomal would lead to an overall cost of [commercial in confidence figure removed] with an overall budget impact over the 5-year period of [commercial in confidence figure removed]. Basic sensitivity analysis suggests the budget impact could range from [commercial in confidence figures removed] over the 5-year time horizon. The budget impact analysis is subject to considerable uncertainty based around patient numbers, the prevalence and incidence values, uptake rates and eligible subpopulation.
Additional factors to consider	Arikayce® liposomal has been designated as an orphan medicine by the European Medicines Agency. AWTTC considers Arikayce® liposomal to be eligible to be considered as an ultra-orphan medicine.

This assessment report is based on evidence submitted by Insmed Ltd and an evidence search conducted by AWTTC on 29 April 2021 and 4 May 2021.

2.0 BACKGROUND

2.1 Condition and clinical practice

Non-tuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* Complex (MAC) is a serious and rare condition with an estimated prevalence of 0.9 per 100,000 in Wales[1-3]. It is characterised by progressive lung damage that can significantly increase morbidity and mortality. Symptoms of MAC-NTM lung disease vary and can include chronic or recurring cough, haemoptysis, shortness of breath, fatigue, night sweats, weight loss, and chest pain. These symptoms become more pronounced as disease advances, alongside the development of severe, permanent lung damage[3,4]. The disorder is also known to contribute to an increasingly impaired quality of life affecting physical, psychological and social functioning[5]. Predisposing risk factors for MAC-NTM include smoking and underlying lung disease such as bronchiectasis or chronic obstructive pulmonary disease (COPD)[4].

There are currently no other licensed treatments for MAC-NTM lung disease. The American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) and the British Thoracic Society (BTS) have developed treatment guidelines[6]. The BTS guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD) currently recommend an oral multi-drug regimen (MDR), a combination of a macrolide (azithromycin or clarithromycin), ethambutol and rifamycin which continues for 12 months after sputum cultures become negative[7]. In clarithromycin-resistant MAC-NTM lung disease the combination of rifampicin, ethambutol and isoniazid (with pyridoxine) or moxifloxacin is recommended. The guideline also includes recommendations to consider the addition of intravenous amikacin or off-label amikacin solution for injection given by nebulisation in severe MAC-NTM lung disease[7].

In 2020, the ATS, European Respiratory Society, European Society of Clinical Microbiology and IDSA (ATS/ERS/ESCMID/IDSA) clinical practice guideline recommended the addition of Arikayce® liposomal to treatment in adult patients with MAC-NTM lung disease who remain culture positive after six months of guideline-based MDR[8]. Disease remission varies depending on patient age and comorbidities; however, recurrence is common, with the majority of cases due to reinfection rather than relapse[3].

2.2 Medicine

Arikayce® liposomal was granted marketing authorisation by the European Medicines Agency (EMA) in October 2020 for the treatment of nontuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis (CF). It should be used in conjunction with other antibacterial agents active against MAC lung infections.

Arikayce® liposomal is a novel, inhaled, once-daily formulation of amikacin; it is an established aminoglycosidic antibiotic. Arikayce® liposomal consists of amikacin sulfate encapsulated in liposomes made of dipalmitoylphosphatidylcholine and cholesterol[4]. The mechanism of action of Arikayce® liposomal is the same as that for all aminoglycosides. It binds to bacterial 30S ribosomal subunits, interferes with an initiation complex between messenger RNA and the 30S subunit resulting in inhibition of protein synthesis and bacterial growth[9]. While aminoglycosides administered intravenously are limited by poor penetration into lung tissue, Arikayce® liposomal technology instead directs a greater concentration of amikacin sulfate to the lungs by inhalation, allowing it to be more readily taken up by the lung macrophages where MAC resides[4].

The recommended dose of Arikayce® liposomal is one vial (590 mg amikacin sulfate) administered once daily by oral inhalation using the Lamira® Nebulizer System[9]. Treatment, as part of a combination antibacterial regimen, should be continued for 12 months following sputum culture conversion (SCC), however, if SCC is not confirmed by six months, treatment should not be continued. Maximum duration of treatment with Arikayce® liposomal should not exceed 18 months[9].

2.3 Comparators

The comparator included in the company's submission is guideline-based oral MDR. This includes different combinations of azithromycin, ethambutol, rifampin, rifabutin, clarithromycin and isoniazid.

Arikayce® liposomal should be used in conjunction with other antibacterial agents active against *Mycobacterium avium* Complex lung infections[9].

2.4 Guidance and related advice

- Treatment of nontuberculous mycobacterial pulmonary disease: an official The American Thoracic Society/ European Respiratory Society/European Society of Clinical Microbiology/ Infectious Diseases Society of America (ATS/ERS/ESCMID/IDSA) clinical practice guideline (2020)[8]
- British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD) (2017)[7]
- An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases (2007)[6]

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, Arikayce® liposomal is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that Arikayce® liposomal may be supplied by a home healthcare provider.

3.0 CLINICAL EFFECTIVENESS

The company submission includes the pivotal phase III, open-label trial INS-212 (CONVERT) comparing the efficacy and safety of daily Arikayce® liposomal added to guideline-based MDR with guideline-based MDR alone in patients with treatment refractory MAC-NTM lung disease[10]. Treatment refractory was defined as patients who did not achieve negative sputum cultures after a minimum of six consecutive months of a background MDR. The company submission also includes a phase III open-label extension to CONVERT, INS-312[11].

3.1 CONVERT

This pivotal open-label, multicentre, randomised phase III study was designed to compare the efficacy and safety of Arikayce® liposomal plus guideline-based MDR with guideline-based MDR alone in adult patients with NTM lung infections caused by MAC (n = 336)[10]. Eligible patients were 18 years or older with MAC-NTM lung disease defined as having MAC-positive sputum or bronchoscopy cultures within the six months prior to screening and at screening. Patients with CF were excluded from the study[4]. Guideline-based MDR consisted of at least two antibiotics based on either the ATS/IDSA guidelines for NTM lung disease or local MAC-NTM lung disease guidelines. Patients were stratified according to smoking status and guideline-based MDR use at

screening (either on-treatment or off-treatment for at least three months prior to screening). Patients who had not achieved SCC (defined as three consecutive monthly MAC-negative sputum cultures) while being treated with guideline-based MDR that had been administered for a minimum duration of six consecutive months prior to study entry were randomly assigned in a 2:1 ratio to receive Arikayce® liposomal once daily plus guideline-based MDR (n = 224) or guideline-based MDR alone (n = 112)[4]. Mean patient age (standard deviation) was 64.7 years (9.8 years). Most patients were female (69.3%), white (69.9%) and had an underlying lung disease such as bronchiectasis (62.5%). A proportion of patients had clarithromycin-resistant MAC (21.8%). Sputum specimens were collected at screening, baseline, at months 1–6, months 8 and 12, and at end of treatment[10].

The primary endpoint was the proportion of patients achieving SCC by month six on-treatment. This was also the US Food and Drug Administration (FDA) approved primary outcome. Patients who achieved SCC at month six remained in the study to receive 12 months of treatment starting from the first of three negative cultures that defined SCC (up to 16 months treatment in total). Patients who did not achieve SCC by month six were discontinued from the study at month eight (when the month six culture results were available) and were offered to enrol in the open label extension, Study INS-312[10]. The EMA approved primary outcome included sustained SCC assessed at least three months off-treatment without intervening relapse or reinfection[4]. Culture conversion was considered sustained if there were no MAC-positive agar cultures and no more than two consecutive MAC-positive monthly broth cultures from SCC through an additional 12 months of treatment, after completing all MAC treatment. Relapse or recurrence was defined as having MAC-positive sputum cultures in broth media (agar negative) for three or more consecutive months or having at least one MAC-positive sputum culture on agar media after SCC[4].

The primary outcome, achieving SCC by month six, was met in 65/224 (29%) of the Arikayce® liposomal plus guideline-based MDR group compared with 10/112 (8.9%) of the guideline-based MDR group (4.22 adjusted odds ratio; 95% CI:
2.08 to 8.57; $p < 0.001$; Table 1). Kaplan-Meier estimates for the distribution of time to SCC by treatment group indicated that Arikayce® liposomal plus guideline-based MDR was nearly four times as likely to achieve SCC compared with guideline-based MDR alone (3.90 hazard ratio; 95% CI: 2.00 to 7.60)[4].

For the EMA approved primary outcome, 36/224 (16.1%) of the Arikayce® liposomal plus guideline-based MDR group achieved sustained culture conversion after three months off-treatment compared to 0/112 of the guideline-based MDR group ($p < 0.0001$; Table 1). At 12 months post-treatment, 30/224 (13.4%) of the Arikayce® liposomal plus guideline-based MDR group achieved sustained culture conversion compared to 0/112 of the guideline-based MDR group[4]. The EMA did not consider the company definition of sustained culture conversion to be appropriate and requested serial data on the culture results. Based on post-hoc analysis that eliminated patients with negative cultures at study baseline and which counted any post-treatment positive culture as positive, 30/224 (13.4%) in the Arikayce® liposomal plus guideline-based MDR group and 0/112 (0%) in the guideline-based MDR group achieved sustained SCC at three months off-treatment. Rates at 12 months off-treatment were 25/224 (11%) and 0/112 (0%), respectively[4,9].

Table 1. Primary outcomes as requested by different regulatory agencies

Outcome	Intention to treat population	
	Arikayce® liposomal plus guideline-based MDR (n = 224)	Guideline-based MDR alone (n = 112)
Proportion of patients achieving SCC by month six on-treatment; requested by FDA and CONVERT primary endpoint	65	10
	4.22 adjusted odds ratio 95% CI: 2.08 to 8.57; p < 0.001	
Sustained SCC assessed at least three months after the end of all treatment (negative sputum culture after three months off-treatment without intervening relapse or reinfection); requested by EMA	36	0
	p < 0.0001	
CI: confidence interval; EMA: European Medicines Agency; FDA: US Food and Drug Administration; MDR: multi-drug regimen; SCC: sputum culture conversion		

The secondary outcomes at six months included comparisons between treatment groups in distance achieved in the 6-minute-walk test (6MWT), time to culture conversion (data not reported), EQ-5D-3L (data not reported) and change in St George's Respiratory Questionnaire (SGRQ)[10]. The SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived wellbeing in patients with obstructive airways disease; it has not been validated in NTM lung disease[7,12]. When reported, significance was not found for any of these outcomes. When comparing 6MWT results at six months, a significantly greater improvement was seen for SCC patients (16.8 m [-10.2 to 43.8]) compared with non-SCC patients (-7.9 m [-30.5 to 14.7]), regardless of treatment group (p = 0.011)[10].

3.2 CONVERT open-label extension

The open-label extension to CONVERT evaluated long-term safety and tolerability of Arikayce® liposomal once daily plus guideline-based MDR for up to 12 months in patients who had not had SCC of their MAC-NTM lung disease by month six of treatment, or who had a recurrent MAC infection (defined as a positive MAC culture after conversion) by month six of treatment in the CONVERT study (n = 163)[11]. All patients received Arikayce® liposomal plus guideline-based MDR. Secondary objectives included number of patients achieving SCC by month six and number of patients achieving SCC by month 12 (or end of treatment), the time to SCC and the change in 6MWT distance at month six and month 12 (or end of treatment). SCC was achieved by 24/90 (26.7%) by month six and 30/90 (33.3%) by month 12 in patients who had been in the guideline-based MDR alone group in the CONVERT study. SCC was achieved by 7/73 (9.6%) by month six and 10/73 (13.7%) by month 12 in patients who had been in the Arikayce® liposomal plus guideline-based MDR group in the CONVERT study[1,11]. No statistical analysis was presented.

3.3 Comparative Safety

The safety and tolerability of Arikayce® liposomal was collected in the pivotal CONVERT study and the open label extension study. In the CONVERT study more patients in the Arikayce® liposomal group experienced treatment emergent adverse events (TEAEs) than patients in the guideline-based MDR alone group (219/223 [98.2%] and 102/112 [91.1%], respectively). Most TEAEs were of moderate severity in the Arikayce® liposomal plus guideline-based MDR group and mild in the guideline-based MDR alone group. The majority of the TEAEs reported in the Arikayce® liposomal plus guideline-based MDR group were considered to be related to Arikayce® liposomal with onset most frequently reported during the first month of treatment. Most of these TEAEs were respiratory, thoracic and mediastinal disorders and included dysphonia, cough, dyspnoea, haemoptysis and oropharyngeal pain[4]. In the pooled safety analysis pulmonary allergic alveolitis was low: 3.2% in the Arikayce® liposomal group compared to 1.3% in the guideline-based MDR alone. Overall there was a high level of discontinuation of Arikayce® liposomal due to TEAEs while discontinuation of treatment due to TEAEs in the guideline-based MDR group was low[10,11]. Adverse events associated with systemic exposure such as nephrotoxicity, tinnitus, hearing impairment and vestibular disorders were low although more common in the Arikayce® liposomal group plus guideline-based MDR compared to guideline-based MDR alone group[10].

The Committee for Medicinal Products for Human Use (CHMP) considered prolonged Arikayce® liposomal treatment (up to 20 months) to relatively low serum levels of amikacin constitutes a risk for developing systemic aminoglycoside-related toxicities[4]. The CHMP noted that appropriate risk minimisation measures were put in place including MAC-NTM lung disease patients being managed in specialised centres to help ensure safe and effective use of Arikayce® liposomal within its licensed indication[4]. This also includes a patient alert card to inform patients that the use of Arikayce® liposomal may be associated with the development of allergic alveolitis[4]. Additional precautions and monitoring are outlined in the Summary of Product Characteristics[9]. In January 2021 a Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety update on aminoglycosides and increased risk of deafness in people with mitochondrial mutations was issued[13].

3.3 AWTTC critique

- Antibiotics for NTM-lung disease caused by MAC are limited and there is an unmet need for additional antimicrobial options for this indication. Arikayce® liposomal is the first licensed treatment for MAC-NTM lung disease[4].
- Welsh clinical experts sought by AWTTC indicate that amikacin solution for injection can be administered off-label via the nebulised route (in addition to guideline-based therapy MDR), if MAC-NTM lung disease fails to respond to MDR alone. Off-label nebulised amikacin was not considered to be a comparator by the company.
- Welsh clinical experts indicate the 2020 updated ATS/ERS/ESCMID/IDSA NTM treatment guideline, which recommends adding Arikayce® liposomal to treatment (in addition to guideline-based MDR), is relevant to clinical practice[8].
- The primary endpoint of the pivotal CONVERT study was a microbiological outcome and there were limited patient orientated outcomes, such as survival and quality of life measurements. The clinical benefit of achieving on-treatment SCC therefore remains uncertain[4]. The EMA approved primary outcome was different to the CONVERT study as CHMP noted if SCC is sustained throughout and after stopping treatment there would be a clear benefit to the patient since no further lung damage due to MAC would be expected and the burden and side effects of MAC treatment regimens would be removed[4].

- Guideline-based MDR was not optimised at baseline in the CONVERT study and may have included non-adherent or inadequately treated patients prior to study entry[4]. The CHMP noted the overall study population was not limited to people who had failed to respond to what could be considered an adequate treatment regimen for MAC-NTM lung disease[4].
- In the CONVERT study the magnitude of sustained post-treatment effects of Arikayce® liposomal plus guideline-based MDR (at month three after 12 months of treatment) is limited[4]. A clinical NTM expert group advised CHMP that this effect might still be clinically relevant in a selected population such as patients with intractable disease, whose disease has already failed to respond to guideline-recommended first-line regimens and where very limited treatment options remain[4].
- Arikayce® liposomal treatment duration may last up to 18 months if SCC occurs at month six. Due to tolerability concerns some patients may find it difficult to continue the full treatment course.
- Significant local tolerability and systemic safety issues are associated with Arikayce® liposomal treatment[4]. Taking into account the modest efficacy and safety concerns, CHMP concluded that Arikayce® liposomal could only be approved for use in a limited patient population and under the supervision of specialists in the management of MAC-NTM lung disease[4].
- The mechanism of resistance to amikacin in mycobacteria has been linked to mutations in the rrs gene of the 16S ribosomal RNA. The CONVERT and open label extension study included only patients with amikacin-sensitive MAC-NTM lung disease[9].

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing Arikayce® liposomal (590 mg once daily by oral inhalation) as an add-on to guideline-based MDR (based on a weighted-average of five MDRs using a combination of azithromycin, ethambutol, rifampin, clarithromycin, rifabutin and isoniazid) to guideline-based MDR treatment alone in adult patients with MAC-NTM lung disease with limited treatment options who do not have CF[1].

The CUA takes the form of an individual patient microsimulation health-state-transition model, with 1-month cycles, a lifetime horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at a rate of 3.5% where the time horizon exceeds one year. The submission incorporates a Wales Patient Access Scheme discount (WPAS). The model comprises five health states: MAC-positive (at least two positive sputum culture tests within the last three tests, with four weeks between the tests), MAC-negative (three consecutive negative sputum culture tests with four weeks between tests), microbiological cure, surgery and death. Patients enter the model in the MAC-positive health state with refractory MAC-NTM lung disease and can then transition to other health states. If they respond to treatment, they transition to the MAC-negative health state based on parametric survival functions fitted to CONVERT study data[10]. After 12 months in the MAC-negative state, patients transition to the microbiological cure health state (sustained SCC), and all MAC-related treatment is assumed to stop. Patients who do not respond to Arikayce® liposomal treatment after six months are considered non-responders and remain in the MAC-positive state and Arikayce® liposomal treatment is suspended. If patients experience a recurrence they can transition to the MAC-positive health state from either the MAC-negative health state based on exponential distributions fitted to CONVERT study data[10] or from the

microbiological cure health state based on annual transition rates from a European study[14]. While on-treatment, patients can experience adverse events and/or discontinue treatment. Patients who continue to be MAC-positive after being treated with guideline-based MDR may need surgery to remove the most damaged areas of the lung in an attempt to improve lung functioning and, if surgery-eligible, they can transition to the surgery health state and receive a surgical treatment option (however, no surgery is assumed to occur in the base case).

The mean adherence rate for Arikayce® liposomal is set to 86% based on the CONVERT trial[10]. The same adherence rate is assumed for MDR. Discontinuation risk is set to an annual rate of 46.4% and includes all-cause discontinuation (including adverse events) as observed in the pivotal trial[10]. Mortality is based on age- and gender-specific mortality rates obtained from 2017 to 2019 UK national life tables, adjusted for MAC status (positive or negative) using a standardised mortality rate based on Kaplan-Meier curves from a Danish registry study[15]. The model further assumes that 22.6% of deaths in the MAC-positive and MAC-negative states are due to MAC-NTM lung disease[16], and reduces the mortality rate by this amount when patients reach the microbiological cure health state.

Guideline-based MDR treatment composition was based on published evidence[17] and included different drug combinations of azithromycin, ethambutol, rifampin, rifabutin, clarithromycin and isoniazid at an average weighted cost of £4.81 per day. Furthermore, 11.52% of patients are eligible to receive IV aminoglycosides[18] at a monthly cost of £1,599.59[19]. Management costs for adverse events included cost per TEAE (dysphonia, cough, dyspnoea and pulmonary exacerbation) taken from published sources. UK costs associated with other healthcare resource use were taken from a retrospective observational physician survey to estimate direct medical costs in Canada, France, Germany, and the UK among refractory patients with MAC lung disease[17]. Healthcare costs for patients in the MAC-negative state were assumed to be 36.6% lower than for patients in the MAC-positive state[17].

Utility data by converter status and stratified by treatment arm over various time points were based on post-hoc analyses of EQ-5D data collected as part of the pivotal trial[10]. Disutilities were applied for adverse events.

Extensive deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to test the influence of the uncertainty of individual parameters on the model results.

4.2 Results

The results of the base case are detailed in Table 2. When compared with guideline-based MDR, the incremental cost-effectiveness ratio (ICER) generated is [commercial in confidence figure removed] per QALY gained (based on WPAS price). The higher cost for Arikayce® liposomal is predominantly driven by the higher acquisition costs though this is partially offset by lower healthcare costs.

Table 2. Results of the base case analysis

	Arikayce® liposomal + guideline-based MDR	Guideline-based MDR only	Difference
Medicine acquisition costs	¶¶	£15,894	¶¶
Administration costs	£0	£0	£0
Healthcare costs (including hospitalisation, aminoglycoside treatment and adverse events)	¶¶	£98,318	¶¶
Total costs	¶¶	£114,212	¶¶
Total QALYs	8.64	7.96	0.68
Total Life Years	10.67	10.52	0.15
ICER (£/QALY gained)	¶¶		

¶¶: commercial in confidence figure removed

ICER: incremental cost-effectiveness ratio; MDR: multi-drug regimen; QALY: quality-adjusted life-year

In deterministic sensitivity analysis, the ICERs for Arikayce® liposomal plus guideline-based MDR compared to guideline-based MDR alone ranged from [commercial in confidence figures removed] and Arikayce® liposomal plus guideline-based MDR dominated when a time horizon of six months was applied. The ICER is most sensitive to Arikayce® liposomal cost and adherence, time horizon and health state utilities. The results are presented in Table 3.

Probabilistic sensitivity analyses indicate that Arikayce® liposomal plus MDR has a 4% and 8% probability of being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Table 3. Results of scenario analyses

Scenarios	ICER	Plausibility
Varying discount rate between 0% and 6%	¶¶	This scenario is plausible as it is based on standard ranges used for sensitivity analysis.
Changing mortality risk based on published evidence[20]	¶¶	This scenario is plausible as it is based on alternative published evidence from a German study.
No mortality reduction for microbiological cure health state	¶¶	This scenario is implausible as it can be assumed that mortality would reduce upon cure.
30% higher mortality reduction for microbiological cure health state	¶¶	The plausibility of this scenario is uncertain as it is based on an assumption.
Surgery option included in the MAC positive state	¶¶	This scenario is plausible as surgery is an option for refractory patients in the MAC positive state.
Utilities averaged across treatment arms of CONVERT trial and applied to both model arms	¶¶	This scenario is plausible as it assumes the same utility values by outcome regardless of treatment arm.
Treatment stopped after non-response for 9 months	¶¶	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
Treatment stopped after non-response for 12 months	¶¶	The plausibility of this scenario is uncertain as it is unclear upon what evidence the change was based.
6-month time horizon	¶¶	This scenario is less plausible since the longer-term benefits associated with successful Arikayce® liposomal treatment may not be observed during this shorter time horizon.
10-year time horizon	¶¶	This scenario demonstrates that the benefits associated with successful Arikayce® liposomal treatment rely on longer-term extrapolation of short-term data in order to reduce the ICER.
Varying treatment adherence rate	¶¶	The plausibility of this scenario is uncertain as it is based on an assumption.
Arikayce® liposomal discontinuation rate varied +/- 20%	¶¶	The plausibility of this scenario is uncertain as it is based on an assumption.
Unit costs varied by +/- 20%	¶¶	The plausibility of this scenario is uncertain as it is based on an assumption.
Alternative recurrence rates based on published evidence[14]	¶¶	This scenario is plausible as it is based on alternative published evidence.
Recurrence rates based on CONVERT trial[10] for first year off-treatment for subsequent years	¶¶	This scenario is plausible as it is based on alternative published evidence from a German study.
Recurrence rate based on CONVERT trial only[10]	¶¶	The plausibility of this scenario reflects the recurrence rates observed in the CONVERT patient population, but may be limited by a shorter follow-up duration.
Different parametric models used for sputum culture conversion varied	¶¶	These scenarios are less plausible as they represent alternative functions with lower fit.
Relapse rate from MAC negative health state varied by +/- 20%	¶¶	The plausibility of this scenario is uncertain as it is based on an assumption.
¶¶: commercial in confidence figure removed		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model and the individual patient, microsimulation, health-state-transition model designed to account for patient and pathway heterogeneity is well presented and appears robust and well-structured.
- The company has made an effort to use the best available data.

Limitations:

- While the model appears robust and well-constructed, the complexity of coding makes it difficult to check and duplicate processes for appraisal purposes.
- While the sample size in the pivotal trial is sufficient[10], the data used to populate individual model health states relies on smaller subsets of patients which could introduce bias if sample size is low.
- The CUA is based on data from the CONVERT study[10]. Due to the differences in delivery modes between the Arikayce® liposomal and the oral guideline-based MDR, this was an open-label study which may introduce bias.
- Adherence rate to Arikayce® liposomal treatment is based on US product shipping data on file[21]. This may not reflect the true adherence, as shipping or dispensing data is not an indication of whether patients are actually taking the medication at home. It is also unclear if these data would accurately reflect Welsh practice.
- Furthermore, the same adherence rate is assumed for the comparator in the absence of data. This will introduce bias. However, the company states that this would represent a conservative assumption.
- The annual discontinuation rate is based on the 6-month rate observed in the pivotal study[10] which is assumed to be constant over time. This may overestimate discontinuation.
- Whilst the utility data was based on the patient responses to the EQ-5D-3L from the CONVERT study, recently published data on the psychometric validation of the EQ-5D-3L in the CONVERT patient population reported poor responsiveness of the EQ-5D-3L to clinically meaningful changes in patients with MAC-NTM lung disease, which could lead to an underestimation of the QALY gain and cost-effectiveness[22]. However, this is based on a post-hoc analysis from the same patient population and thus may introduce bias and lacks in external validity.
- Disease-specific mortality data is based on the Danish population of MAC-NTM lung disease patients between 1997 and 2008[15]. It is unclear whether this would be reflective of current Welsh patients and how much bias any generalisability issues may introduce.
- The model only considers the costs and benefits of one cycle of treatment with Arikayce® liposomal and does not take into account retreatment with Arikayce® liposomal after recurrence. This may underestimate treatment costs and effects if repeat treatment cycles upon recurrence were to be used in routine practice.
- Costs associated with other healthcare resource use was taken from a retrospective observational physician survey to estimate direct medical costs in Canada, France, Germany, and the UK among refractory patients with MAC-NTM lung disease[17]. This study included 38 patients in the UK in 2015 which were used to estimate the healthcare cost. The low number of patients may affect generalisability and introduce bias.

- Use of Arikayce® liposomal will require training of patients and carers by the initiating healthcare professional. This additional resource use and cost is not taken into account in the model because the company state that training would either be undertaken as part of routine care or funded by the company as part of their Homecare Plus Programme.
- Renal function monitoring is recommended in the Summary of Product Characteristics due to potential nephrotoxicity of amikacin[9]. This cost was not taken into account in the model. However, the company states that blood tests were included in the model and as part of the maintenance of treatment and normal monitoring of guideline-based treatment and no further monitoring cost is expected.
- Furthermore, the model requires a lot of time to run which may explain why the base case is based on 100 patients and 30 replications only which seems low and could introduce uncertainty into the results.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of Arikayce® liposomal (590 mg once daily by oral inhalation) as an add-on to guideline-based MDR (based on a weighted-average of five MDR using a combination of azithromycin, ethambutol, rifampin, clarithromycin, rifabutin and isoniazid) to guideline-based MDR treatment alone in adult patients with MAC-NTM lung disease with limited treatment options who do not have CF.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates an annual prevalence of MAC-NTM lung disease in Wales of 12 patients, with an annual incidence of 9 new patients per year. These estimates are based on a prevalence rate of MAC-NTM lung infections of 0.9 per 100,000 people[2] and an incidence rate of 0.67 per 100,000 which was adapted from UK data[23] and applied to the Welsh population under the assumption that 43% of NTM lung disease patients will suffer from MAC-NTM lung disease[24,25].

Considering a mean duration of treatment with Arikayce® liposomal of 7.7 months[10], only newly incident patients are assumed to receive treatment each year. Taking into account a mortality rate of 8% in this patient group[20], this results in a total number of 11 patients on-treatment in Year 1 and eight patients per year in the remaining four years of the 5-year time horizon of the analysis. Of these patients, 53% are assumed to receive guideline-based MDR treatment[24], of which 30% will be refractory to guideline-based MDR treatment[25,26]. Seventy percent of the refractory patients are then assumed to be eligible to receive Arikayce® liposomal, resulting in [commercial in confidence figure removed] per year on-treatment in Wales. Based on the unmet need in this patient population, the company estimates an uptake rate of 100% from Year 1. Taking into account a treatment discontinuation rate of 46% taken from the pivotal trial[10], this results in [commercial in confidence figure removed] receiving Arikayce® liposomal in Year 1, and [commercial in confidence figure removed] in Years 2 to 5. However, in order to round to full patient numbers, it is assumed that [commercial in confidence figure removed] receive treatment in Year 1 and [commercial in confidence figure removed] per year in subsequent years. Annual costs [commercial in confidence figure removed] were applied for Arikayce® liposomal and [commercial in confidence figure removed] for guideline-based MDR.

Basic sensitivity analysis was undertaken, altering patient numbers based on UK prevalence estimates and treatment duration and changing the acquisition cost by +/- 20%.

5.2 Results

The budget impact is presented in Table 4. It is estimated that introducing Arikayce® liposomal would lead to an overall cost of [commercial in confidence figure removed] with an overall budget impact over the 5-year period of [commercial in confidence figure removed]. Basic sensitivity analysis suggests budget impact to be in the range from [commercial in confidence figure removed] over the 5-year time horizon.

Table 4. Company-reported costs associated with use of Arikayce® liposomal as an add-on to guideline-based therapy based on a weighted-average of five multidrug regimes (MDR) using a combination of azithromycin, ethambutol, rifampin, clarithromycin, rifabutin and isoniazid to MDR treatment alone in adult patients with nontuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) with limited treatment options who do not have cystic fibrosis

	2021	2022	2023	2024	2025
Sub-population of eligible patients (indication under consideration)	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Medicines acquisition costs in a market with new medicine*	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs) including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figure removed *This includes cost of Arikayce® and cost of guideline-based MDR to reflect add-on guideline-based MDR when Arikayce® is prescribed.					

The company estimates that net resource implications arising from the introduction of Arikayce® liposomal will lead to a saving of £6,547 in Year 1, decreasing to £3,274 in subsequent years. This is mainly a consequence of savings in hospitalisation and outpatient care costs[17]. These resource-type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact. The company has also factored discontinuation growth and mortality into the calculations.
- There is uncertainty regarding the number of patients in the eligible sub-population. It is unclear why the prevalence for Wales of 0.9 per 100,000 population is considerably lower than the UK prevalence of 6.38 per 100,000 population[23]. Welsh clinical experts indicate eligible patients are likely to be [commercial in confidence figure removed]. In order to gauge the budget impact of potentially higher patient numbers, AWTTC ran a scenario analysis assuming a 100% increase in uptake which would result in [commercial in confidence figure removed] treated in Year 1 and [commercial in confidence figure removed] thereafter with a budget impact of [commercial in confidence figure removed] in Year 1 and [commercial in confidence figure removed] in subsequent years with a total budget impact of [commercial in confidence figure removed] over the 5-year period.
- The budget impact is calculated based on a mean duration of treatment (7.7 months) observed in the CONVERT trial. If Arikayce® liposomal is used for a minimum of 12 months (the recommended duration if SCC occurs at month six[9]) with a maximum treatment duration of 18 months, budget impact will increase to [commercial in confidence figure removed] for the 5-year period, respectively.
- It is unclear whether the budget impact includes cost of renal monitoring as recommended by the Summary of Product Characteristics[4].

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 Medicines developed to treat rare diseases

The applicant company suggests that Arikayce® liposomal should be considered as an ultra-orphan medicine.

AWTTC does consider Arikayce® liposomal eligible to be appraised as an ultra-orphan equivalent medicine. The medicine has EMA designated orphan status due to the prevalence of MAC-NTM lung disease being below the ceiling for orphan designation, 5 people in 10,000[4]. Welsh clinical expert opinion indicates that the full population of the licensed indication in Wales is below the ceiling for ultra-orphan status of ≤ 1 in 50,000 people in Wales.

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 5) if they consider Arikayce® liposomal is a medicine developed to treat a rare disease.

Table 5. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
Severity of the disease	MAC-NTM lung disease can be chronic, progressive and life-threatening condition. Patients with MAC-NTM lung disease experience debilitating symptoms such as shortness of breath, fever, weight loss, loss of appetite, blood in the sputum and fatigue. MAC-NTM lung disease accelerates the decline in pulmonary function and is associated with a reduced health-related quality of life.
Unmet need	Arikayce® liposomal is the first licensed therapy for the treatment of NTM lung infections in adults caused by MAC. There is a significant unmet need due to the absence of any other licensed treatments for this patient population; a frequent lack of treatment efficacy with guideline-based MDR and the severe morbidity and mortality that ensues as the disease progresses.
Innovative nature of the medicine	The applicant company claims that Arikayce® liposomal uses an innovative active principle[10] to overcome the existing limitations of intravenously administered antibiotics e.g. amikacin, that includes unfavourable safety profile. Arikayce® liposomal is delivered by a novel inhalation device, the Lamira® Nebulizer System that enables amikacin to reach a patient's lungs in therapeutically increased concentrations, with reduced potential for aminoglycoside-specific side effects.
Societal impact on non-health benefits that may not adequately be captured in the QALY	MAC-NTM lung disease can reduce physical functioning, decrease general health perceptions and impair social functioning as well as increase bodily pain and decrease energy and vitality[5]. The company state symptoms such as coughing and fatigue cause exhaustion which interferes with everyday life and patients' ability to work[27]. The company anticipate the use of Arikayce® liposomal will have a positive effect on caregiver burden.
Does the medicine cure or reverse rather than stabilise the condition?	The company suggests that considering the limited treatment options in the target population, Arikayce® liposomal offers MAC-NTM patients an add-on therapy option with a proven chance of a microbiological cure for their serious illness.
Does medicine bridge a gap to a definitive therapy?	The medicine does not bridge a gap to a definitive therapy.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; CF: cystic fibrosis; MAC: *Mycobacterium avium* Complex; MDR: multi-drug regimens; NMG: New Medicines Group; NTM: nontuberculous mycobacterial	

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