NICE advice

Antimicrobial prescribing: nebulised liposomal amikacin

Evidence summary
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Product overview

The content of this evidence summary was up to date in May 2021. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Nebulised liposomal amikacin (amikacin liposomal nebuliser dispersion, Arikayce, Insmed) is an aminoglycoside antibiotic that is given by oral nebulisation once daily. It has a marketing authorisation for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* complex in adults with limited treatment options, who do not have cystic fibrosis.

Likely place in therapy

Nebulised liposomal amikacin may be an option for treating non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* complex in adults with limited treatment options, and who do not have cystic fibrosis. It should be used in combination with other antimicrobial agents active against *Mycobacterium avium* complex lung infections. Treatment should not continue

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for more than 6 months if sputum culture conversion has not been confirmed by then. *Mycobacterium avium* complex (MAC) includes *Mycobacterium avium*, *Mycobacterium intracellulare* and *Mycobacterium chimaera*. Nebulised liposomal amikacin is not licensed for treating NTM lung infections caused by other mycobacterial species.

One randomised controlled trial (RCT), Griffith et al. (2018), in adults with non-cystic fibrosis MAC lung disease, found that the addition of nebulised liposomal amikacin to guideline-based antimicrobial therapy led to statistically significantly more people having sputum culture conversion (defined as 3 consecutive months with a negative sputum culture in the study) by month 6, compared with guideline-based antimicrobial therapy alone.

Nebulised liposomal amikacin is associated with adverse effects, particularly pulmonary effects (including allergic alveolitis) and systemic effects (including nephrotoxicity, ototoxicity and effects on neuromuscular conditions), that may be due to long-term use of amikacin (European public assessment report [EPAR] for nebulised liposomal amikacin). See the summary of product characteristics (SPC) for nebulised liposomal amikacin for full details on warnings and precautions for use, including monitoring recommendations (such as monitoring auditory, vestibular and renal function). 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.

The SPC states that nebulised liposomal amikacin, as part of a combination antimicrobial regimen, should be continued for 12 months after sputum culture conversion. The maximum duration of treatment should be no longer than 18 months. It should be started and managed by specialists experienced in treating MAC lung disease (see the SPC for nebulised liposomal amikacin).

The NICE guideline on antimicrobial stewardship makes recommendations on the effective use of new antimicrobials.

Factors for decision making

Effectiveness and safety

Evidence was from 1 randomised controlled trial (RCT; Griffith et al. 2018, n=336) and a 12-month open-label extension study (Winthrop et al. 2020, n=163). Griffith et al. (2018) included adults without cystic fibrosis and with amikacin-sensitive active *Mycobacterium avium* complex (MAC) lung disease despite at least 6 months' treatment with guideline-based antimicrobial therapy. Winthrop et al. (2020) included patients from the Griffith et al. (2018) study who did not have sputum culture

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conversion by month 6. All participants received nebulised liposomal amikacin plus guideline-based antimicrobial therapy in this study and there was no primary efficacy outcome.

In Griffith et al. (2018), statistically significantly more patients had sputum culture conversion by month 6 of treatment (primary outcome) with nebulised liposomal amikacin plus guideline-based antimicrobial therapy than with guideline-based antimicrobial therapy alone (29.0% compared with 8.9%, adjusted odds ratio 4.22, 95% confidence interval [CI] 2.08 to 8.57, p<0.001). There was also a statistically significant improvement in sustained culture conversion 3 months after treatment was stopped in the amikacin group compared with the control group (16.1% compared with 0%, p<0.0001); results reported from the European public assessment report (EPAR).

Based on their analysis, the EPAR concluded that approximately 12% of people who start nebulised liposomal amikacin in addition to a combination antimicrobial regimen may have sustained culture conversion that is maintained for 3 months after completing 12 months' treatment (from the first negative culture that defined conversion).

In Griffith et al. (2018), there was no statistically significant difference between the 2 groups for the change from baseline for the 6-minute walk test. Also, the difference between the 2 groups for the mean change in St George's Respiratory Questionnaire score from baseline to month 6 was less than the minimal clinically important difference of 4 units.

In Winthrop et al. (2020), within the prior-amikacin group, 9.6% had culture conversion after 6 months in the study (up to 14 months' amikacin treatment in total) and 13.7% after 12 months in the study (up to 20 months' amikacin treatment in total). In the amikacin-naive group, 26.7% and 33.3% had culture conversion after 6 and 12 months in the study respectively.

In Griffith et al. (2018), 98.2% of patients in the nebulised liposomal amikacin plus guideline-based antimicrobial therapy group had a treatment-emergent adverse event compared with 91.1% in the guideline-based antimicrobial therapy alone group. The most common adverse events were respiratory, thoracic and mediastinal disorders (87.4% in the amikacin group compared with 50.0% in the control group). In the nebulised liposomal amikacin group, 17.5% stopped taking amikacin because of a treatment-emergent adverse event.

In Winthrop et al. (2020), in the prior-amikacin group (participants who had amikacin in the Griffith et al. 2018 study), 8.2% stopped amikacin because of a treatment-emergent adverse event, compared with 24.4% in the amikacin-naive group.

See the summary of product characteristics (SPC) for contraindications, cautions and a general

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summary of the safety profile.

Limitations of the evidence

Griffith et al. (2018) was an open-label RCT and the risk of bias was rated as high. The primary outcome for the study was microbiological, and limited patient-oriented outcome data were available. Winthrop et al. (2020) was a non-comparative study with no primary efficacy outcome.

Adults in the Griffith et al. (2018) study had active MAC lung disease despite at least 6 months' treatment with guideline-based therapy. The EPAR states that the guideline-based therapy was not optimised at baseline, and some participants may have received inadequate treatment before study entry. Overall, the study population was not limited to people whose condition had not responded to an adequate antimicrobial treatment regimen for MAC (EPAR).

Griffith et al. (2018) was powered for the primary outcome of sputum culture conversion by month 6 of treatment. The EPAR states that the benefit of on-treatment sputum culture conversion remains uncertain and unquantified. In contrast, if culture conversion is sustained throughout and after stopping treatment there is a clear benefit because no further lung damage from MAC would be expected and the burden of MAC treatment regimens is removed.

Taking into account the difficulty in managing MAC lung disease, the EPAR concluded that the 'modest treatment benefit would only support a very restricted approval, for use in adults with limited treatment options, who do not have cystic fibrosis'.

Person-centred factors

Nebulised liposomal amikacin is given once a day using the Lamira nebuliser system. Treatment may last for up to 18 months if there was a sputum culture conversion response in the first 6 months. This long-term commitment may have an impact on some people's daily life. The EPAR states that 'the data demonstrate the poor tolerability' of nebulised liposomal amikacin. This means that some patients may not be able to continue the full treatment course.

Antimicrobial resistance

The mechanism of resistance to amikacin in mycobacteria has been linked to mutations in the rrs gene of the 16S ribosomal RNA (see the SPC for nebulised liposomal amikacin). The studies reviewed in this evidence summary only included people with amikacin-sensitive MAC lung disease. The environmental impact of nebulised liposomal amikacin using this delivery system was

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not assessed in the studies included in this evidence review.

Resource implications

The cost of nebulised liposomal amikacin is £9,513 for a pack of 28 vials (28-day supply, MIMs, April 2021). Each pack of 28 vials also contains the Lamira nebuliser handset and 4 aerosol heads (see the SPC). The dosage recommended in the SPC is 1 vial (590 mg amikacin) once daily.

Treatment for 6 months would cost £61,155, and for 18 months would be £183,465 (based on a 30-day month).

See the full evidence review for more information.

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