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ADIS DRUG Q&A

Amikacin Liposome Inhalation Suspension in Refractory *Mycobacterium avium* Complex Lung Disease: A Profile of Its Use

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Abstract
Amikacin liposome inhalation suspension (ALIS) [Arikayce® Liposomal (EU); Arikayce® (USA)], a liposomal suspension of the aminoglycoside amikacin (590 mg) for nebulization via the Lamira® Nebulizer System, is available as add-on therapy for treatment-refractory *Mycobacterium avium* complex (MAC) lung disease in adults who have little or no alternative treatment options. Its addition to guideline-based therapy (GBT) significantly improved the likelihood of achieving sputum culture conversion (defined as three consecutive monthly MAC-negative sputum cultures) by month 6 relative to GBT alone in adults with treatment-refractory MAC lung disease, with the conversion response maintained over up to 12 months' therapy and at 3 months' post treatment in significantly higher proportions of ALIS plus GBT than GBT alone recipients. ALIS as an add-on therapy to GBT was associated with an increased risk of respiratory adverse reactions compared with GBT alone, but treatment-emergent adverse events associated with systemic amikacin exposure were uncommon.

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1 What is the Rationale for Using Amikacin Liposome Inhalation Suspension (ALIS) in Refractory *Mycobacterium avium* Complex (MAC) Lung Disease?

Nontuberculous mycobacterial (NTM) infection usually presents as lung disease, particularly in individuals with underlying structural airway disorders (e.g. bronchiectasis, chronic obstructive pulmonary disease) [1]. Among the species most commonly involved in NTM lung disease are several members of *Mycobacterium avium* complex (MAC), including *M. avium* and *Mycobacterium intracellulare*. Treating NTM lung disease requires the use of multiple antibacterial agents over a prolonged period and is frequently associated with clinically relevant adverse events (AEs) [1]. Moreover, outcomes are often suboptimal, with recurrence (relapse or reinfection with another strain or species) common [1, 2].

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Parenteral aminoglycosides are among only a few options currently available for intensifying standard oral MAC lung disease therapy, with add-on parenteral amikacin or streptomycin (to the initial treatment regimen) recommended for patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC lung disease by the 2020 American Thoracic Society (ATS)/European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of NTM lung disease [1]. Their use, however, is often limited due to the high risk of systemic AEs (e.g. renal and auditory toxicities) [1]. As an alternative to parenteral therapies, various inhaled therapies have demonstrated increased therapeutic drug concentrations within the lungs along with a reduced incidence of off-target AEs (owing to limited overall systemic exposure) [3].

Amikacin liposome inhalation suspension (ALIS) [Arikayce® Liposomal (EU); Arikayce® (USA)], formerly known as liposomal amikacin for inhalation (LAI), is a suspension of liposome-encapsulated amikacin for nebulization, providing targeted drug delivery to the lungs and minimal systemic exposure [4]. This article provides an overview of the use of ALIS as add-on therapy for treatment-refractory MAC lung disease in adults, with a summary of its prescribing information in the EU and the USA provided in Table 1. Unless otherwise specified, ALIS contains 590 mg of amikacin.

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Adis evaluation of add-on ALIS in refractory MAC lung disease
Increases the likelihood of achieving sputum culture conversion by month 6
Maintains the conversion response during continued therapy and post-treatment
Acceptable tolerability profile; associated with a risk of respiratory adverse reactions

2 How Does ALIS Work?

Amikacin (the active ingredient of ALIS) inhibits bacterial protein synthesis by binding to the 30S bacterial ribosome subunit [5, 6]. It has established bactericidal activity against a broad spectrum of Gram-positive and -negative bacteria [7], and has demonstrated potent in vitro activity against clinical isolates of MAC and other NTM species [8, 9].

In vitro, ALIS effectively penetrated *M. avium* biofilms and subsequently reduced the viable cell count, in a concentration-dependent manner, at concentrations ≥ 16 μg/mL [10]. Compared with free amikacin, ALIS enhanced the uptake of amikacin into macrophages (one of the cells NTM can persist within) both in vitro and in vivo [10] and more effectively reduced *M. avium* and *Mycobacterium abscessus* cell counts in vitro [11]. Of note, in preclinical studies, the uptake of ALIS into macrophages did not compromise macrophage function [12].

3 Is ALIS Associated with Resistance?

In MAC, acquired resistance to amikacin is based on alterations (e.g. mutations in the *rrs* gene of 16S rRNA) to the 30S ribosome subunit (i.e. the drug target) and is mostly observed in patients extensively exposed to amikacin and/or related aminoglycosides [1, 9]. The minimum inhibitory concentration (MIC) breakpoint for resistance is ≥ 128 μg/mL for ALIS (vs ≥ 64 μg/mL for parental amikacin) [13].

In a multinational, phase 3 study (CONVERT) in adults with treatment-refractory MAC lung disease [14], 23 (10.3%) of 224 patients receiving ALIS plus guideline-based therapy (GBT) and 3 (2.7%) of 112 patients receiving GBT alone had MAC isolates with post-baseline amikacin MICs of > 64 μg/mL; MICs of < 64 μg/mL were subsequently reported in 5 and 2 of these patients, respectively. Two ALIS plus GBT recipients (vs 0 GBT alone recipients) achieved culture conversion despite post-baseline amikacin MICs of > 64 μg/mL, although one subsequently had a MAC isolate with an amikacin MIC of > 64 μg/mL [14].

4 What are the Pharmacokinetic Properties of ALIS?

The nebulization process results in a combination of liposomal and free amikacin being delivered [5]. Following once-daily administration of ALIS in 59 patients with MAC lung disease participating in CONVERT, median sputum amikacin concentrations 1–4 h post-inhalation were 426, 242 and 414 μg/g at 1, 3 and 6 months, respectively, and were highly variable [15]. According to population pharmacokinetic modelling of CONVERT data ($n = 39$), systemic amikacin exposure was low following the once-daily inhalation of ALIS for 6 months [median maximum concentration and area under the concentration–time curve from 0 to 24 h ($AUC_{0–24}$) values of 1.85 mg/L and 16.7 mg·h/L], with the upper range values (6.87 mg/L and 55.6 mg·h/L) below that seen with parenteral amikacin (77 mg/L and 548 mg·h/L). Moreover, the difference between day 1 and month 6 median $AUC_{0–24}$ values was < 10%, suggesting that the systemic amikacin exposure is similar regardless of the treatment duration of ALIS. Of note, serum amikacin exposure was similar between Caucasian and Japanese patients [15]. Unabsorbed ALIS in the lungs is likely eliminated via cellular turnover and expectoration [5].

5 What is the Efficacy of ALIS?

The potential of ALIS as add-on therapy to GBT was initially evaluated in a multinational phase 2 study in adults with treatment-refractory NTM (MAC or *M. abscessus*) lung disease [16]. Patients were randomized to receive ALIS or placebo (empty liposomes), both inhaled once daily, in addition to ongoing GBT for 84 days (double-blind period), after which they could all receive ALIS plus GBT for 84 days (open-label period). Although the addition of ALIS to GBT did not provide a statistically significant benefit over placebo plus GBT in terms of the primary endpoint (change from baseline to day 84 on a semi-quantitative mycobacterial growth scale), the proportion of patients achieving ≥ 1 negative sputum culture (31.8% vs 8.9%; nominal $p = 0.006$) and the change from baseline in the 6-minute walk test (6MWT) distance (+20.6 m vs −25.0 m; nominal $p = 0.017$) at day 84 was significantly higher with ALIS ($n = 44$) compared with placebo ($n = 45$) [16].

A subsequent randomized, open-label, multinational, phase 3 study (CONVERT) demonstrated the efficacy of adding ALIS to GBT in adults with treatment-refractory

Table 1 Prescribing summary of add-on amikacin liposome inhalation suspension in adults with *Mycobacterium avium* complex lung disease in the EU [6] and the USA [5]

What are the approved indications for ALIS?	
EU	For use in conjunction with other antibacterial agents for the treatment of non-tuberculous mycobacterial lung infections caused by MAC in adults with limited treatment options who do not have cystic fibrosis
USA[a]	For use as part of a combination antibacterial drug regimen for the treatment of MAC lung disease in adults who have not achieved negative sputum cultures despite ≥ 6 consecutive months of a multidrug background regimen therapy and who have limited or no alternative treatment options
	Approved using the Limited Population pathway
How is ALIS available?	
As a liposome suspension of amikacin in a unit-dose vial for oral inhalation; each vial contains 590 mg of amikacin	
How should ALIS be stored?	
Refrigerate vials at 2–8 °C (36–46 °F) until their expiration date; do not freeze	
Store at a controlled [up to 25 °C (77 °F)] room temperature for up to 4 weeks, then discard	
What is the recommended dosage of ALIS?	
Once-daily inhalation of the nebulized contents of one vial; use only the Lamira® Nebulizer System	
Treat for 12 months following sputum culture conversion (maximum treatment duration of 18 months); do not continue treatment beyond 6 months if sputum culture conversion is unconfirmed at that point (EU)	
How should ALIS be administered?	
Ensure the vial is at room temperature before use; shake the vial until the contents appear uniform and well mixed prior to opening, then pour the contents into the medication reservoir of the nebulizer handset	
If a dose is missed, administer the next dose the next day; do not double the dose to make up for the missed dose	
Pts using a bronchodilator should use it before administering ALIS	
Consider pretreating pts with a history of (EU) or known (USA) asthma, bronchospasm, COPD (USA) or [hyper- (USA)] reactive airway disease (EU) with a short-acting bronchodilator (EU) or selective beta-2 agonist (USA)	
Consider pretreating pts with evidence of bronchospasm subsequent to ALIS therapy with bronchodilators (EU)	
How should ALIS be used in special populations?	
Pts who are, or become, pregnant	No data; preferable to avoid during pregnancy (EU); advise of the potential risk to a foetus (systemic exposure to aminoglycosides may be associated with total, irreversible, bilateral congenital deafness) [USA]
Pts who are breast-feeding	No data; consider benefits of breast-feeding, clinical need for ALIS and/or any potential adverse effects of drug or maternal MAC lung disease on breast-fed infant
Pts aged < 18 years	Efficacy and safety not established
Pts aged ≥ 65 years	No dosage adjustments required (EU); similar efficacy and safety to pts aged < 65 years, but monitor renal function (USA)
Pts with hepatic impairment	No data; no dosage adjustments required (as amikacin is not hepatically metabolized)
Pts with renal impairment	No data; monitor pts with known or suspected renal impairment (USA)
Pts with non-refractory MAC lung disease	Use is not recommended (USA)

Unless otherwise indicated, information applies to both the EU and the USA. Consult local prescribing information for further details

ALIS amikacin liposome inhalation suspension, *COPD* chronic obstructive pulmonary disease, *MAC Mycobacterium avium* complex, *pts* patients

[a]This was an accelerated approval based on the achievement of sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by month 6 in clinical studies [5]

MAC lung disease [14] and is the focus of this section. CONVERT enrolled patients who met ATS/IDSA criteria for MAC lung disease; had active disease (as documented by MAC-positive sputum or bronchoscopy cultures within 6 months prior to screening and at screening) despite stable GBT for ≥ 6 months; and who were currently receiving GBT or who had stopped GBT < 12 months prior to screening. Patients with active pulmonary tuberculosis, cystic fibrosis, or MAC isolates with amikacin resistance (i.e. MICs of > 64 µg/mL) were among those excluded. The assignment of patients to randomized treatment arms (ALIS inhaled once daily using a nebulizer as add-on therapy to GBT, or GBT alone) was stratified by prior GBT (on treatment or post-treatment for 3–12 months) and smoking status (current or not). Patients were treated for an initial 6 months, with those who achieved culture conversion by and who remained culture-negative at month 6 remaining in the study and completing 12 months' therapy from the first month that defined culture conversion (for a total of up to 16 months' therapy), after which they were followed (post-treatment)

Table 2 Efficacy of add-on amikacin liposome inhalation suspension in adults with treatment-refractory *Mycobacterium avium* complex lung disease in CONVERT [14]

Comparators (no. of evaluable pts)	% of pts achieving culture conversion by month 6[a] [adjusted OR; 95% CI]	LSM Δ from BL at month 6 in 6MWT distance (m) [mean BL value]
ALIS + GBT vs GBT alone (224 vs 112)	29.0 vs 8.9 [4.22; 2.08–8.57]*	−1.5 vs 1.5 [424.2 vs 421.0]

ALIS amikacin liposome inhalation suspension, *BL* baseline, *GBT* guideline-based therapy, *LSM* least-squares mean, *OR* odds ratio, *pts* patients, *6MWT* 6-minute-walk test, *Δ* change

*$p < 0.001$ vs GBT alone

[a]Primary endpoint

for 12 months [14]. Patients (from either treatment group) who failed to achieve culture conversion by month 6 and who exited the study at month 8, and those who had recurrent MAC infection (i.e. a positive MAC culture following conversion) by month 6 that was confirmed at month 8 were eligible for an open-label, multinational, phase 3 extension study [17]. In CONVERT, the use of bronchodilators before the administration of ALIS (for patients who developed bronchospasm), dose interruptions [for the management of treatment-emergent AEs (TEAEs)] and rescue medication (parenteral amikacin and streptomycin) was permitted, although patients receiving rescue medication were required to withdraw from the study following its use [14].

The primary efficacy endpoint was the proportion of patients achieving culture conversion [defined as three consecutive monthly MAC-negative sputum cultures (including all sputum samples collected at each visit)] by month 6 [14]. Although a recent in vitro study has suggested that MAC isolate growth in sputum samples is not affected by residual amikacin [18], in CONVERT, sputum samples were collected at each monthly visit and on each of the two days preceding the visit, with patients refraining from administering ALIS starting two days prior to the scheduled visit and recommencing following sputum collection on the day of the visit (thereby ensuring that the sputum collected was obtained up to 72 h after the last dose) [14]. Indeed, sputum amikacin concentrations at 48–72 h post-inhalation are ≈ 5% of those seen 1–4 h post-inhalation [5, 6]. Baseline patient demographics and disease characteristics were generally well balanced between the ALIS plus GBT ($n = 224$) and GBT alone ($n = 112$) groups, although the proportion of female patients was 73.7% and 60.7% and the median duration of MAC lung disease was 4.5 and 3.3 years. Overall, 89.9% of the 336 patients were either receiving GBT at the time of enrolment or had not been receiving GBT for < 3 months and 89.3% were not current smokers [14]. At baseline, GBT included a macrolide (93.3% of patients), a rifamycin (86.3%) or ethambutol (81.4%), with 55.6% of patients receiving GBT consisting of a macrolide plus a rifamycin plus ethambutol [5]. Analyses were conducted in the intent-to-treat population [14].

5.1 What are the Benefits of Adding ALIS to Guideline-Based Therapy?

The addition of ALIS to GBT significantly improved the proportion of patients achieving culture conversion by month 6 versus GBT alone, indicating that an ALIS plus GBT recipient would be more than fourfold more likely to achieve culture conversion than a GBT alone recipient (Table 2) [14]. A treatment effect was seen early; the cumulative proportion of patients in the ALIS plus GBT and GBT alone groups achieving culture conversion were 15.2% and 8.0% by month 3 (i.e. patients who achieved the first of three consecutive negative sputum cultures at month 1), 23.7% and 8.9% by month 4 and 27.2% and 8.9% by month 5 [14].

In ALIS plus GBT recipients, culture conversion rates were generally similar across patient subgroups based on baseline amikacin MICs (for MAC isolates) of 8–64 µg/mL (28.6–34.5%), but were low for those with baseline or post-baseline amikacin MICs of > 64 µg/mL (0–8.7%) [14]. It is worth noting that culture conversion was achieved by 13.7% of 51 patients in the ALIS plus GBT group and 4.5% of 22 patients in the GBT alone group with clarithromycin-resistant MAC isolates (i.e. MICs of ≥ 32 µg/mL) [14].

In terms of the secondary endpoints (which were assessed in a hierarchical manner), there was no significant difference between the ALIS plus GBT and GBT alone groups in the least-squares mean (LSM) change from baseline at month 6 in the 6MWT distance (Table 2) [14]. Thus, statistical significance was not tested for the subsequent endpoints [time to culture conversion and change from baseline at month 6 in the St George's Respiratory Questionnaire (SGRQ) score] [19]. However, according to a prespecified exploratory analysis, patients (in either treatment group) who achieved culture conversion ($n = 70$) showed a significantly greater LSM change from baseline in the 6MWT distance than those who did not achieve culture conversion ($n = 191$) [+16.8 m vs −7.9 m (mean baseline values of 457.9 m and 427.7 m); nominal $p = 0.011$] [14]. Of note, the LSM change from baseline at month 6 in the SGRQ score was 4.2 in ALIS plus GBT recipients and 0.4 in GBT alone recipients (LSM difference of 3.8; 95% CI 0.67–6.94) [14].

5.2 And are These Benefits Durable?

Add-on therapy with ALIS displayed durable efficacy in CONVERT [5, 6]. Significantly ($p < 0.0001$) higher proportions of patients in the ALIS plus GBT group than the GBT alone group achieved culture conversion by month 6 and maintained this conversion (defined as consecutive negative sputum cultures with no positive culture on solid media or ≤ 2 consecutive positive cultures on liquid media following culture conversion) through the completion of 12 months' post-conversion therapy [18.3% (41/224) vs 2.7% (3/112)] and at 3 months' post treatment [16.1% (36/224) vs 0% (0/112)] [5, 6]. Results from a post hoc analysis [in which patients with negative cultures (solid or liquid media) at study baseline were eliminated and those with post-treatment positive cultures (solid media or broth) were considered positive] of data at 3 months' post therapy were consistent with those of the primary analysis, with 13.4% (30/224) of patients in the ALIS plus GBT group and 0% (0/112) of those in the GBT alone group maintaining culture conversion [6]. At 12 months' post treatment, culture conversion had been maintained in 11.2% (25/224) and 0% (0/112) of patients, respectively [6].

Data from the CONVERT extension study were consistent with those from CONVERT and suggest that longer-term (> 6 months) ALIS plus GBT may result in additional patients achieving culture conversion [17]. All patients in the CONVERT extension study received ALIS plus GBT for 12 months (median treatment duration of 11.6 months). The use of bronchodilators before the administration of ALIS (for patients who developed bronchospasm), dose interruptions (for the management of respiratory AEs) and rescue medication [aminoglycosides with MAC activity (e.g. kanamycin, streptomycin)] was permitted, although patients receiving rescue medication were required to withdraw from the study following its use. Culture conversion by months 6 and 12 was achieved by 26.7% and 33.3% of 90 patients originally treated with GBT alone in the core study and by 9.6% and 13.7% of 73 patients originally treated with ALIS plus GBT in the core study. In the prior ALIS cohort, total ALIS exposure at months 6 and 12 was ≤ 14 months and ≤ 20 months, and the mean ALIS exposure from baseline of the core study to culture conversion in the extension study was 11.5 months. Culture conversion rates in patients in the ALIS-naïve cohort with clarithromycin-susceptible, -intermediate or -resistant isolates (defined as MICs of ≤ 8 µg/mL, 16 µg/mL and ≥ 32 µg/mL, respectively) [$n = 70$, 3 and 17] were 37.1%, 33.3% and 17.3%, respectively. Following culture conversion, relapse and reinfection was reported in five and four patients in the ALIS-naïve cohort and in none and three patients in the prior ALIS cohort. In terms of the 6MWT distance endpoint, there was no improvement from baseline to month 6 or 12, nor did there appear to be a demonstrated benefit between converters and non-converters in either cohort [17].

6 What is the Tolerability of ALIS?

As add-on therapy to GBT, ALIS had an acceptable tolerability profile in adults with treatment-refractory MAC lung disease participating in CONVERT [14]. TEAEs occurred in 98.2% of 223 ALIS plus GBT recipients and 91.1% of 112 GBT alone recipients, with 82.5% of the TEAEs in the ALIS plus GBT group considered by the investigator to be related to ALIS. Most TEAEs in the ALIS plus GBT and GBT alone groups were moderate and mild in severity, respectively. The most frequently reported TEAEs in CONVERT were respiratory in nature; such TEAEs occurred in 87.4% and 50.0% of patients receiving ALIS plus GBT or GBT alone and were mostly mild to moderate in severity. Of note, the US prescribing information carries a boxed warning regarding an increased risk of respiratory adverse reactions, including hypersensitivity reactions, bronchospasm, exacerbation of underlying pulmonary disease, and haemoptysis (Table 3) [5]. TEAEs reported in ≥ 10% of patients and occurring in more ALIS plus GBT recipients than GBT alone recipients were dysphonia (45.7% vs 0.9%), cough (37.2% vs 15.2%), dyspnoea (21.5% vs 8.9%), haemoptysis (17.5% vs 13.4%), fatigue (16.1% vs 7.1%), diarrhoea (12.6% vs 4.5%), nausea (11.2% vs 3.6%) and oropharyngeal pain (10.8% vs 1.8%). Most of these TEAEs were initially observed within the first month of ALIS plus GBT therapy, with the incidence of new onset declining thereafter; they infrequently (≤ 3.1% of patients each) resulted in the discontinuation of ALIS [14].

TEAEs associated with systemic amikacin exposure were uncommon, and those related to renal and urinary disorders (haematuria, leukocyturia and proteinuria) were infrequent in both the ALIS plus GBT and GBT alone groups (1.3% vs 4.5% of patients) [14]. Ototoxicity-related TEAEs reported in CONVERT and occurring in more ALIS plus GBT recipients than GBT alone recipients were tinnitus (7.6% vs 0.9% of patients; most were mild to moderate in severity), dizziness (6.3% vs 2.7%), balance disorder (1.3% vs 0%), vertigo (0.9% vs 0%) and presyncope (0.4% vs 0%). Of note, six tinnitus TEAEs resulted in an interruption to ALIS therapy and one led to discontinuation, but half of the observed events resolved with continued ALIS treatment [14].

Serious TEAEs were reported in 20.2% of ALIS plus GBT recipients and 17.9% of GBT alone recipients, with most being respiratory in nature [14]. In the ALIS plus GBT group, 17.5% of patients discontinued ALIS because of TEAEs. Overall, 2.7% of ALIS plus GBT recipients and 4.5% of GBT alone recipients experienced TEAEs (mostly respiratory in nature) leading to death [14].

Table 3 Summary of the warnings and precautions for add-on ALIS in adults with *Mycobacterium avium* complex lung disease in the EU [6] and the USA [5]

What are the contraindications to the use of ALIS?	
Coadministration with any aminoglycoside administered via any route of administration (EU); pts with severe renal impairment (EU)	
What other special warnings/precautions/monitoring requirements pertain to the use of ALIS?	
Increased risk of respiratory adverse reactions	Includes hypersensitivity pneumonitis[a], bronchospasm[b], exacerbation of underlying pulmonary disease[c] and haemoptysis
	Exercise caution and discontinue use if signs of exacerbation are seen in pts with COPD, infective exacerbation of COPD and infective exacerbation of bronchiectasis (EU)
	Manage pts with bronchospasm, exacerbation of underlying pulmonary disease or haemoptysis as medically appropriate (USA)
	Discontinue use in pts with allergic alveolitis (EU) or hypersensitivity pneumonitis (USA) and manage pts as medically appropriate
Anaphylaxis and hypersensitivity reactions	Discontinue use and manage pts as medically appropriate
	Evaluate pts for previous hypersensitivity reactions to aminoglycosides prior to initiation of ALIS
Ototoxicity	Includes deafness, dizziness, presyncope, tinnitus and vertigo
	Closely monitor pts with known or suspected auditory or vestibular dysfunction; periodically monitor auditory or vestibular function in all pts (EU)
	Manage pts as medically appropriate
Nephrotoxicity	Closely monitor pts with known or suspected renal dysfunction; periodically monitor renal function in all pts (EU)
Neuromuscular blockage	Closely monitor pts with known or suspected neuromuscular disorders; use not recommended in patients with myasthenia gravis (EU)
What clinically relevant drug interactions may potentially occur with ALIS?	
Drugs with neurotoxic, nephrotoxic or ototoxic potential (e.g. ethacrynic acid, furosemide, intravenous mannitol)	Avoid concomitant use

Unless otherwise indicated, information applies to both the EU and the USA. Consult local prescribing information for further details

ALIS amikacin liposome inhalation suspension, *COPD* chronic obstructive pulmonary disease, *pts* patients

[a]Reported as allergic reaction to ALIS, allergic alveolitis, pneumonitis and interstitial lung disease (USA)

[b]Reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnoea, exertional dyspnoea, prolonged expiration, throat tightness and wheezing (USA)

[c]Reported as COPD, infective exacerbation of COPD and infective exacerbation of bronchiectasis (EU and USA)

In the CONVERT extension study, no new safety signals indicative of cumulative ototoxicity or nephrotoxicity were identified with ≤ 20 months of total ALIS exposure in the prior ALIS cohort, and the safety profile of ALIS plus GBT in the ALIS-naïve cohort was generally similar to that of the ALIS plus GBT group in CONVERT (i.e. most TEAEs were respiratory in nature and consistent with MAC lung disease, underlying comorbidities and the administration of an inhaled drug) [17]. TEAES were seen in 100% and 93.2% of patients in the ALIS-naïve and prior ALIS cohorts (n = 90 and 73), with the most common (incidence > 15%) being respiratory TEAEs of special interest (ALIS-naïve cohort: dysphonia, cough and dyspnoea in 43.3%, 35.6% and 17.8% of patients, respectively; prior ALIS cohort: haemoptysis in 15.1% of patients). TEAEs of special interest associated with systemic amikacin exposure (ototoxicity, nephrotoxicity, and neuromuscular disorders) were infrequent in both cohorts; the MedDRA preferred terms reported in ≥ 5% of patients were hearing loss, tinnitus, dizziness and haematuria (7.8%, 6.7%, 5.6% and 5.6%, respectively) in the ALIS-naïve cohort and hearing loss and haematuria (9.6% and 5.5%) in the prior ALIS cohort. Most TEAEs in the two cohorts were mild to moderate in severity; as expected, severe or life-threatening TEAEs (35.6% vs 19.2% of patients), serious TEAEs (35.6% vs 27.4%) and TEAEs resulting in the discontinuation of ALIS (24.4% vs 8.2%) occurred in more patients adding ALIS to GBT (i.e. the ALIS-naïve cohort) compared with those continuing ALIS plus GBT (i.e. the prior ALIS cohort). TEAEs resulting in death occurred in 4.4% and 2.7% of patients in the respective groups [17].

7 What is the Current Clinical Position of ALIS in MAC Lung Disease?

MAC lung disease is difficult to treat and associated with an impaired quality of life [2]. Recurrence is common and in such patients treatment options are limited [2]. While the benefits of intensifying standard oral therapy by adding a parenteral aminoglycoside for ≥ 2–3 months outweigh the risks in patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC lung disease, such intensification is limited by the renal, auditory and vestibular toxicity associated with systemic amikacin use [1]. The targeted delivery of amikacin (via nebulization) to the lungs may improve the drug's efficacy and decrease (owing to reduced systemic exposure) the toxicity seen with parenteral administration [1]. In the 2020 ATS/ERS/ESCMID/IDSA clinical practice guideline for the treatment of NTM lung disease [1], the addition of ALIS to the treatment regimen is recommended for patients with MAC lung disease who have failed therapy (i.e. remain sputum culture positive) after ≥ 6 months of GBT [1].

Although a clinical benefit has yet to be demonstrated with the addition of ALIS to GBT, a microbiological response has been shown, suggesting that ALIS is a useful treatment option for this patient population. In the clinical setting, ALIS as add-on therapy to GBT:

- Increases the likelihood of achieving sputum culture conversion by month 6, with the conversion response maintained during continued therapy and post-treatment.
- Effective against MAC isolates regardless of baseline amikacin MICs of 8–64 μg/mL; less effective against those with baseline or post-baseline amikacin MICs of > 64 μg/mL.
- Acceptable tolerability profile; associated with an increased risk of respiratory adverse reactions, but TEAEs associated with systemic amikacin exposure are uncommon.

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