27 October 2020
EMADOC-1700519818-518626
EMA/OD/0000030955
Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

Arikayce liposomal (Amikacin sulfate)

Treatment of nontuberculous mycobacterial lung disease

EU/3/14/1259

Sponsor: Insmed Netherlands B.V.

**Note**

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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# 1. Product and administrative information

| | |
|---|---|
| **Product** | |
| Active substances at the time of orphan designation | Amikacin sulfate |
| International Non-Proprietary Name | Amikacin |
| Tradename | Arikayce liposomal |
| Orphan condition | Treatment of nontuberculous mycobacterial lung disease |
| Sponsor's details: | Insmed Netherlands B.V.<br>Stadsplateau 7<br>3521 AZ Utrecht<br>Netherlands |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | Insmed Limited |
| COMP opinion date | 6 February 2014 |
| EC decision date | 8 April 2014 |
| EC registration number | EU/3/14/1259 |
| **Post-designation procedural history** | |
| Transfer of sponsorship | Transfer from Insmed Limited to Insmed Netherlands B.V. – EC decision of 21 February 2019 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | Jayne Crowe / Ewa Balkowiec Iskra |
| Applicant | Insmed Netherlands B.V. |
| Application submission date | 1 July 2019 |
| Procedure start date | 18 July 2019 |
| Procedure number | EMA/H/C/005264 |
| Invented name | Arikayce liposomal |
| Proposed therapeutic indication | Treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis.<br><br>Further information on Arikayce liposomal can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/arikayce-liposomal |
| CHMP opinion date | 23 July 2020 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteur(s) | Nikolaos Sypsas / Eva Malikova |
| Sponsor's report submission date | 4 March 2020 |
| COMP discussion | 8-10 September 2020 |
| COMP opinion date | 10 September 2020 |

# 2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing amikacin sulfate was considered justified based on the established clinical efficacy of amikacin as active substance in the proposed condition, and on preclinical data with the sponsor's liposomal formulation for inhalation showing high eradication rates of nontuberculous mycobacterial infection in the lungs;
- the condition is chronically debilitating due to progressive lung damage in severe forms that respond poorly to treatment;
- the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing amikacin sulfate may be of significant benefit to those affected by the condition. The sponsor presented early clinical data showing better lung penetration and lower incidence of side effects as compared to the existing intravenous formulation. The Committee considered that this can translate into a clinically relevant advantage for patients affected by nontuberculous mycobacterial lung disease, as there are well-known and documented side-effects of the existing intravenous formulation that limit its use. In addition, the possibility of using amikacin by inhalation has the potential to result in a major contribution to patient care by allowing the outpatient administration of the product.

# 3. Review of criteria for orphan designation at the time of marketing authorisation

## Article 3(1)(a) of Regulation (EC) No 141/2000

***Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made***

**Condition**

The therapeutic indication "Treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis" falls within the scope of the designated orphan condition "Treatment of nontuberculous mycobacterial lung disease".

Non-Tuberculous Mycobacterial (NTM) disease refers to those cases of clinical infection caused by Mycobacteria other than Mycobacterium Tuberculosis. There are many species of NTM, many of which are not implicated in human infection and disease. Mycobacterium avium complex (MAXC) is by far the most common NTM responsible of pulmonary disease in humans, followed by M. abscessus, M. fortuitum and M. kansasii.

NTM pulmonary disease manifests often as primarily upper lobe fibrocavitary disease. In addition to lung manifestations, lymphatic, skin/soft tissue, and disseminated disease can occur. The diagnosis

can be complex, as often the recovery of a single isolate from the airways does not necessarily prove the causative role of the recovered mycobacteria in the on-going lung infection and disease, also because the clinical manifestations are not specific and the affected patients have additional comorbidities and are therefore often colonized by multiple different microorganisms.

**Intention to diagnose, prevent or treat**

The medical plausibility was confirmed by the positive benefit/risk assessment of the CHMP. Please see EPAR.

**Chronically debilitating and/or life-threatening nature**

There have been no changes in the seriousness of the condition since the time of orphan designation. NTM lung disease is a chronic condition requiring complex and lengthy treatments consisting of multi-drug regimen of which some drugs are not well tolerated by affected patients, in particular if the disease is severe or in patients having failed prior treatment attempts. The chronic disease often leads to progressive inflammation and even to lung damage.

The prognosis of NTM lung disease caused by MAC is poor and is associated with a high mortality risk. Five-year all-cause mortality rates have been reported up to 39.7%

**Number of people affected or at risk**

There have been no changes in the prevalence of the condition since the time of orphan designation. The sponsor concluded with an estimated prevalence of 0.65 per 10,000 inhabitants based on literature searches.

The literature search was first performed including all relevant non-tuberculous mycobacteria (NTM) species, then combined with results for NTM lung disease specifically, and finally restricted to epidemiology data of Europe. While a number of epidemiological publications reported the incidence of the condition, the sponsor retrieved one study of the NTM lung disease prevalence rates in 5 EU countries (France, Germany, Italy, Spain, UK), reporting prevalence rates between 0.59 and 0.65 per 10,000 (Wagner et al., 2014). Additional point prevalence rates for the overall condition NTW were available only for Germany (0.23 per 10,000 in 2009 and 0.33 in 2014) (Ringshausen et al., 2016) and the UK (0.78 in 2006 and 0.47 in 2016 per 10,000) (Axson et al., 2018).

The sponsor used the most conservative figure of 0.65 in 10,000 as the proposed prevalence estimate, which was considered acceptable.

## Article 3(1)(b) of Regulation (EC) No 141/2000

***Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.***

**Existing methods**

There are no approved treatments specifically for NTM or for the subset with MAC lung disease in the EU. Treatment guidelines have been developed by the ATS/IDSA and the British Thoracic Society, which have since been adopted by various countries globally and incorporated into local guidelines. The current treatment of NTM lung disease is primarily with a multi-drug regimen (MDR) based on the

treatment of tuberculosis. The recommendation for patients with MAC is a 3-drug regimen including a macrolide, ethambutol and a rifamycin. Treatment is often for 12 to 18 months and selected based on clinical presentation and disease progression but may exceed 18 months.

Specifically, the ATS/IDSA guidelines recommend a 3 times weekly regimen of clarithromycin (1,000 mg) or azithromycin (500 mg), rifampicin (600 mg) and ethambutol (25 mg/kg) for most patients with nodular/bronchiectatic MAC lung disease. For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (500 to 1,000 mg) or azithromycin (250 mg), rifampicin (600 mg) or rifabutin (150 to 300 mg) and ethambutol (15 mg/kg) with consideration of 3 times weekly IV amikacin or streptomycin early in therapy is recommended. Patients should continue treatment for 12 months after sputum culture conversion (SCC) has been achieved.

The recently updated British Thoracic Society guideline on the management of NTM pulmonary disease provides treatment recommendations similar to the ATS/IDSA guidelines for the NTM species that most commonly fulfil the ATS/IDSA microbiologic criteria for NTM pulmonary disease within the UK, namely MAC, *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. abscessus* complex.

The guidance is based on five randomised controlled studies and several non-comparative studies involving individuals (not known to be HIV-positive) with MAC identified in the literature. The stated aim of treatment is to achieve 12 months of negative sputum cultures while on treatment. SCC on treatment has been reported to occur in the majority of patients without fibrocavitary disease if they complete a full course of guideline-based treatment. In patients who experience treatment failure and/or have more severe underlying conditions such as fibrocavitary disease, it is more difficult to achieve SCC even with extended treatment, and alternative therapeutic options are limited.

Amikacin has been shown to be active against NTM *in vitro*. It has been tested against NTM in samples obtained from > 30,000 patients in England over a 13-year period (2000 to 2014). Furthermore, the majority of clinical NTM isolates (96%) have been found to have amikacin MICs ≤ 32 µg/mL. Inclusion of nebulized rather than parenteral amikacin in systemic treatment regimens has been used off-label in some treatment centres but this is not based on robust evidence from controlled clinical trials.

**Significant benefit**

The significant benefit was argued by the sponsor on the basis of clinical efficacy of Arikayce liposomal in last line patients who did not respond to previous treatments (none of which is specifically authorized for the condition, albeit they are used and recommended in guidelines). Arikayce was used on top of standard of care.

The pivotal study INS-212 tested Arikayce liposomal in combination with standard of care for multi-drug resistant (MDR) in non-CF patients with confirmed NTM lung infection caused by MAC who did not show sputum culture conversion (SCC) to negative after at least 6 months of guideline-recommended antibiotic therapy. The number of treatments varied from 1 to ≥4 at baseline (Table 2), with almost all the study population on a macrolide regimen (equally distributed in the MDR-only arm and the MDR plus Arikayce arm of the study). Approximately 30% of patients were exposed to at least 1 systemic or inhaled aminoglycoside prior to baseline. The MDR duration patient population was on average 3.94 years for the whole patient population.

**Table 1.** Subjects by number of MDR agents at Baseline (ITT population) (from the CHMP report)

| Number of MDR agents | ALIS + MDR N = 224 (%) | MDR alone N = 112 (%) | Total N = 336 (%) |
|---|---|---|---|
| 1 | 1/224 (0.4) | 0 | 1/336 (0.3) |
| 2 | 15/224 (6.7) | 6/112 (5.4) | 21/336 (6.3) |
| 3 | 110/224 (49.1) | 60/112 (53.6) | 170/336 (50.6) |
| ≥4 | 96/224 (42.9) | 45/112 (40.2) | 141/336 (42.0) |

ALIS, amikacin liposome inhalation suspension; ITT, intent-to-treat; MDR, multidrug regimen; N, number

**Table 2.** patients who received at least 1 systemic aminoglycoside and/or inhaled aminoglycoside treatment prior to study Baseline (ITT population) (from the CHMP report)

| Prior exposure to aminoglycoside | ALIS + MDR N = 224 | | MDR alone N = 112 | |
|---|---|---|---|---|
| | n | % | n | % |
| At least 1 prior systemic aminoglycoside and/or inhaled aminoglycoside | 67 | 29.9 | 32 | 28.6 |
| At least 1 prior systemic aminoglycoside | 51 | 22.8 | 20 | 17.9 |
| At least 1 prior inhaled aminoglycoside | 27 | 12.1 | 16 | 14.3 |

ALIS, amikacin liposome inhalation suspension; ITT, intent-to-treat; MDR, multidrug regimen; N, n, number

In the study approximately 1/8 patients who assumed ALIS in addition to MDR achieved and sustained SCC at month 3 after completing 12 months of treatment post-SCC. However, the rate drops to 1/10 by month 12 post-treatment. Some of these patients may have a relapse while others may have a reinfection. It can be expected that adding a single inhaled agent to patients who have failed to respond to prior treatment would have limited efficacy but in a population who failed to respond to recommended regimens, and considering the severity of uncontrolled NTM, and the lack of alternative treatments, this benefit may be important in this patients' subset. For this reason, the use of this product was considered by the EU licencing body (CHMP) to be beneficial in the patient group with no or limited treatment options. The use is recommended under supervision of experts in the field of NTM management.

The COMP considered that significant benefit was supported based on the demonstration of clinical efficacy in patients for whom no or limited treatment options exist.

# 4. COMP position adopted on 10 September 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of nontuberculous mycobacterial lung disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.65 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to progressive lung damage in severe forms that respond poorly to treatment. Five-year mortality rates have been reported up to 40%;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Arikayce liposomal may be of potential significant benefit to those affected by the orphan condition still hold. This is based on clinical data showing that in some patients with non-tuberculous mycobacterial lung infection caused by *Mycobacterium avium* complex and limited treatment options, Arikayce liposomal, used on top of background treatment in last line, resulted in clearance of the mycobacteria from the sputum. The Committee considered that this constitutes a clinically relevant advantage for patients affected by the condition.
- The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:
- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Arikayce liposomal, amikacin sulfate, amikacin, for treatment of nontuberculous mycobacterial lung disease (EU/3/14/1259) is not removed from the Community Register of Orphan Medicinal Products.