



Clinical Commissioning Policy Proposition: Continuous aztreonam lysine for cystic fibrosis (all ages)

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**Clinical Commissioning Policy Proposition:
Continuous aztreonam lysine for cystic fibrosis (all ages)**

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Equality Statement

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Plain Language Summary

Cystic fibrosis (CF) is an inherited disease, caused by a faulty gene. This gene controls movement of salt and water in and out of cells, so the lungs and digestive system become clogged with mucus making it hard to breathe and digest food. CF is the most common, life-limiting, recessively inherited disease in the UK and most cases are now diagnosed soon after birth. Around one in 25 of the population carry the faulty gene.

When people with cystic fibrosis suffer with a build up of mucus in the lungs it can make it difficult to clear the airway and this results in an environment in which bacteria can thrive. Some of these bacteria can cause recurrent lung infections which in turn cause damage to the airways, reducing the patient's ability to breathe freely and seriously impacting on quality of life.

Inhaled antibiotics are used to treat infection and reduce symptoms. Currently, three different antibiotics are used: tobramycin, colistimethate sodium and aztreonam lysine. These are usually used alternately to reduce the risk of developing resistance. Resistance is where a drug is no longer effective because the bacteria adapt and continue to cause symptoms despite treatment.

For a very small number of people living with CF (approximately 1-5%), alternating antibiotic treatment may not be possible due to intolerance or allergy to both tobramycin and colistimethate sodium.

NHS England has concluded that there is insufficient clinical evidence to support the routine commissioning of continuous aztreonam for individuals with cystic fibrosis whose condition cannot be managed with alternating antibiotic treatment.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission continuous inhaled aztreonam lysine.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether continuous inhaled aztreonam lysine for cystic fibrosis patients with chronic pseudomonas aeruginosa infections will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting over 10,000 people across the UK.

It is caused by a genetic mutation; specifically a mutation in a gene call CFTR. The CFTR gene normally creates a protein that regulates levels of sodium and chloride in cells. If the gene is defective, it results in a build up of thick, sticky mucus in the body which is particularly damaging to the lungs, the gut and the pancreas, blocking the airways and the flow of digestive juices in the gut. This can result in problems with the digestion and absorption of food resulting in poor growth, and long-term infection and inflammation in the lungs (which is the main cause of morbidity and mortality).

Current standard treatments for cystic fibrosis aim to minimise the symptoms and include: (i) frequent chest physiotherapy (ii) specialist dietary advice, supplements and enzyme replacement therapy, and (iii) medication to relieve bronchospasm and inflammation in the lungs, reduce the viscosity of mucus in the airways or treat serious infection in the lungs.

Pseudomonas aeruginosa is the most frequent and important pathogen responsible for chronic infection in people with cystic fibrosis. NHS England currently has a formal commissioning policy for the use of inhaled therapies for patients (over the age of 6 years) with cystic fibrosis and chronic pseudomonas aeruginosa infection (A01/P/b 2014). This policy confirms that three antibiotics are funded in sequence: tobramycin, colistimethate sodium and aztreonam lysine. Inhaled tobramycin and aztreonam lysine have been licensed for alternate month use due to theoretical concerns regarding bacterial resistance. As most people with cystic fibrosis will feel worse during the month with no antibiotic cover, alternating regimens are usually prescribed.

Aztreonam lysine is only considered if there is progressive loss of lung function (defined as greater than 2% per year decline in forced expiratory volume (FEV1) as % of predicted) or where there is continued need for intravenous therapy for exacerbations i.e. more than two per year despite therapy with an alternating regimen of tobramycin and colistimethate sodium.

For a small number of patients, alternating treatment with aztreonam and tobramycin or colistimethate sodium may not be suitable due to intolerance or contraindications to both tobramycin and colistimethate sodium. For this subgroup, continuous aztreonam lysine may

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be the only available therapy that achieves adequate symptom relief for sustained periods.

3. Definitions

Cystic fibrosis (CF) is an inherited disease, meaning it is caused by a defect in an individual's genes.

The defective gene that causes CF is called the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR protein helps to produce mucus, which is a mixture of salts, water, sugars and proteins that cleanses, lubricates and protects many passage ways in the body including the lungs and pancreas. In CF, the defective CFTR protein does not allow chloride ions out of mucus-producing cells and the mucus becomes thick and sticky. In the pancreas, clogged passageways prevent secretion of digestive enzymes into the intestine causing serious impairment of digestion and mucus in the lungs may plug the airways preventing good air exchange. The mucus is also a rich source of nutrients for bacteria, leading to frequent infections.

CF is caused by a recessive allele (one of a number of forms of the same gene) inherited from both parents. If a patient has just one copy of the faulty allele, they are a carrier but will have no symptoms.

Pseudomonas aeruginosa is a type of bacteria that can cause long-term *pseudomonas aeruginosa* infection in the lungs and is particularly prevalent in patients with CF due to the symptoms described above.

Inhaled aztreonam, a formulated lysine salt of the original monobactam antibiotic, is approved for the treatment of respiratory symptoms in patients over the age of 6 with cystic fibrosis who are colonised with *Pseudomonas aeruginosa*. Lyophilised aztreonam lysine is diluted with 0.17% sodium chloride and administered using a nebuliser system.

Nebulised aztreonam lysine is licensed for use in patients over the age of 6 years.

4. Aim and Objectives

This policy proposition aims to define NHS England's commissioning position on continuous inhaled aztreonam lysine as part of the treatment pathway for adults and children with cystic fibrosis and chronic *pseudomonas aeruginosa* infections.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults and children with cystic fibrosis and chronic *pseudomonas aeruginosa* infections.

5. Epidemiology and Needs Assessment

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting over 10,000 people. Cystic fibrosis is most common in white people of northern European descent. The condition is much less common in other ethnic groups.

There is currently no cure for cystic fibrosis, but many treatments are available to manage it, including physiotherapy, exercise, medication and nutrition. More than half of the cystic fibrosis patients in the UK will live past age 41 years.

Cystic fibrosis is generally progressive over time as lung tissue becomes more damaged. With age, patients are more likely to need longer courses of medication and longer, more frequent periods in hospital. Severely ill patients may need lung or heart transplants.

Approximately 70% of patients with cystic fibrosis (over the age of 6 years) are prescribed inhaled antibiotics. Consensus of clinical opinion estimates that 1-5% of those patients (c. 45 to 250 patients) may require treatment with continuous aztreonam lysine.

6. Evidence Base

NHS England has concluded that there is insufficient evidence to support the routine commissioning of the continuous use of aztreonam lysine as an option for patients with cystic fibrosis and chronic pseudomonas aeruginosa infections.

This evidence review was concerned with the cost and clinical effectiveness of continuous treatment with aztreonam lysine via a nebuliser, in adults and children with cystic fibrosis who have chronic infection with *Pseudomonas aeruginosa*.

In summary, no published evidence was found for the continuous use of inhaled aztreonam lysine (AZLI). Furthermore there is currently no published evidence comparing continuous aztreonam lysine and cyclical aztreonam lysine (28 days on AZLI followed by 28 days on a different antibiotic).

There is level 1 evidence for the clinical effectiveness of aztreonam lysine (AZLI) to treat infection by *Pseudomonas aeruginosa* (*P. aeruginosa*), compared to a placebo. There is also evidence from one randomised control trial (RCT) to support the superiority in clinical effectiveness of AZLI compared to tobramycin, coming from one RCT. A single study found that AZLI use was more cost effective than tobramycin.

All of the studies examined either a period of 28 days using AZLI or a cycle of using AZLI for 28 days, followed by 28 days with no antibiotics. There is evidence extrapolated from a single level 1 study that 28 days on tobramycin maintains the clinical benefits of 28 days on AZLI.

Clinical Evidence Review Questions

Research question 1: Is continuous treatment with aztreonam lysine via a nebuliser clinically effective in adults and children with cystic fibrosis who have chronic infection with *Pseudomonas aeruginosa*?

There is level 1 evidence for the efficacy of AZLI compared to a placebo. An often used measure of clinical effectiveness is to measure the percentage change, from the baseline value measured before the trial, in forced expiratory volume in 1 second (% change from baseline (%CFB) in FEV1). Three RCTs have all found, at the end of a 28 day trial, an improvement in the %CFB in FEV1 of between 0.3 to 8% in the AZLI arm and a deterioration in the placebo arm of between -2 to -2.5% (McCoy et al. 2008; Retsch-Bogart et al., 2009; Wainwright et al., 2011). Other metrics, such as the change in respiratory symptoms scale of the revised cystic fibrosis questionnaire (CFQ-R RSS) also demonstrate analogous improvements, compared with a placebo.

Likewise there is level 1 evidence that AZLI is superior to TOB, coming from the RCT (Assael et al., 2013), that compared the 75 mg AZLI, taken three times a days, in 28 days on / 28 days off cycles, with a similar TOB treatment. At the end of a 28 day cycle the mean %CFB in FEV1 was 8.4% for AZLI compared with 0.55% for TOB. During the off cycle there was an observed deterioration, but after three cycles there was still an overall improvement of 2.05%, compared with TOB at -0.66%. The study also found that, compared with TOB, patients treated with AZLI had:

- fewer hospitalisations (p=0.044)
- lower CFQ-R RSS scores (p=0.005)
- fewer respiratory events, needing additional antibiotics (p=0.004)

It also should be noted that the trial had an extension in which all patients received AZLI in a 28 days on / 28 days off cycle and there was no difference between the patients who had received TOB/AZLI and those receiving AZLI/AZLI. The deterioration in %CFB in FEV1 during the off periods was observed in all trials. There is also level 2 evidence that the improvement in FEV1 is greater when AZLI is being taken three times a day compared to when it is being taken twice a day (Oermann et al., 2010).

The only RCT identified that examined the continuous use of antibiotics for longer than 28 days was (Trapnell et al., 2012), which used 28 days of AZLI to establish a consistent baseline for a TOB trial. There is evidence extrapolated from a level 1 study that 28 days on TOB maintains the benefits of 28 days on AZLI, but no further improvement in FEV1 is made.

In terms of safety outcomes, patients with chronic *Pseudomonas aeruginosa* infections display a wide range of adverse events. The most common of these is coughing (30-80%), but also pyrexia, oropharyngeal pain, dyspnea and many others. In the majority of trials, there was no statistically significant difference between the rates of adverse events in the trial and placebo arm. One exception to this was (Retsch-Bogart et al., 2009) found AZLI treated patients had a lower incidence of productive cough than placebo treated patients, but this was based on a small sample size (31 of 160 patients) and was not observed in other trials. Likewise there was no statistically significant difference in the numbers of adverse events in patients treated with AZLI, compared with those treated with TOB (Assael et al., 2013).

Research question 2: Is continuous treatment with aztreonam lysine via a nebuliser cost effective in adults and children with cystic fibrosis who have chronic infection with *Pseudomonas aeruginosa*?

One study was found that compared the cost of AZLI, taken three times a day on a 28 day on/28 day off cycle, with an analogous TOB treatment (Schechter et al., 2015). The study found that the total cost over 3 years of AZLI was 16% less than TOB (AZLI: £148,710 TOB: £176,268) [Original figures provided in US dollars and converted to the nearest full pound based on conversion rate on 17/11/2015 of £1 to \$1.52 and is provided as a guideline for comparison only]. This saving was predominantly coming from the assumed reduction in number of hospitalisation, with a slight reduction in drug costs. It was also based on a US healthcare model. The study also found AZLI marginally increased the number of quality adjusted life years.

A final point which is noteworthy is that, with the exception of (Trapnell et al., 2012), all of the RCTs were funded by Gilead, sole manufacturer of Cayston (trademark name for AZLI). Also there was considerable overlap in the authors of the majority of the RCTs and that many of these authors had received grants from Gilead, notably Oermann, McCoy, Retsch-Bogart, Gibson and Wainwright.

7. Documents That Have Informed This Policy Proposition

Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis (A01/P/b 2014)

8. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016)