

Clinical Commissioning Policy Proposition:

Levofloxacin nebuliser solution for
chronic *Pseudomonas* lung
infection in cystic fibrosis (Adults)

Reference: NHS England 1621



First published: **Month Year**

**Prepared by NHS England Specialised Services Clinical Reference Group for
Specialised Respiratory Services**

Published by NHS England, in electronic format only.

Draft for public consultation

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About Cystic Fibrosis

Cystic fibrosis (CF) is the most common, life-limiting, inherited disease in the UK. It affects about 8,823 people in England.

Cystic fibrosis is caused by a single faulty gene that controls the movement of salt in the body. In people with cystic fibrosis, the lungs become clogged with thick, sticky mucus resulting in infections and inflammation that make it hard to breathe. They also have problems digesting food as the thick mucus blocks the release of secretions in to the gut. People with cystic fibrosis can also have other problems including diabetes, infertility and osteoporosis.

About current treatments

Inhaled therapies are used to relieve tightness in airways and inflammation in the lungs, reduce the stickiness of mucus in the airways or treat serious infections in the lungs.

Inhaled antibiotics are a normal treatment for people with cystic fibrosis with chronic lung infection.

About the new treatment

Inhaled levofloxacin is a new antibiotic to provide an extra option for treatment.

What we have decided

NHS England has carefully reviewed the evidence to treat chronic *Pseudomonas* lung infection in cystic fibrosis with Levofloxacin nebulise solution. We have concluded that there is enough evidence to consider making the treatment available.

Draft for public consultation

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission levofloxacin nebuliser solution for chronic *Pseudomonas* lung infection in cystic fibrosis.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

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 levofloxacin nebuliser solution for chronic *Pseudomonas* lung infection in cystic fibrosis will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

2 Proposed Intervention and Clinical Indication

Cystic fibrosis (CF) is the commonest autosomal recessive life-limiting genetic condition in the United Kingdom. Despite modern management the average age of death is still only 29 years. More than 90% of premature deaths are directly due to lung infections. The lungs of people with cystic fibrosis can become infected by bacteria (most commonly *Pseudomonas aeruginosa* (*Pa*)), bacterial infection is rarely eradicated once chronic infection has developed. The guideline on antibiotic treatment for cystic fibrosis from the Cystic Fibrosis Trust (2009) advises that people with cystic fibrosis and chronic pulmonary *Pseudomonas aeruginosa* infection should be recommended for regular nebulised anti-pseudomonal antibiotic treatment. At the time of publication of that guideline, colistimethate sodium and tobramycin were the only nebulised antibiotics licensed for the treatment of chronic *Pseudomonas aeruginosa* infection in people with cystic fibrosis. The guideline recommends that initial treatment should be with nebulised colistimethate sodium with tobramycin as a second-line agent. Subsequently a third inhaled antibiotic has become available - aztreonam lysine and NHS England has published a clinical

policy on the use of all three agents which states that colistimethate sodium should be used first line, tobramycin second line, and aztreonam lysine used third line (<https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf>).

This policy describes the rationale for the use of inhaled levofloxacin in people with cystic fibrosis, the indications for its use and for future monitoring.

3 Definitions

Cystic fibrosis is a genetic condition defined by a mutation in both copies of a person's genes that code for an important protein called CF Transmembrane Conductance Regulator. People with cystic fibrosis typically have lung damage (bronchiectasis), chronic sinus problems, bowel problems (including malabsorption, malnutrition, diarrhoea and constipation), and fertility problems.

Pseudomonas aeruginosa is a bacterial species characterised as being a Gram negative bacillus. Found widely in the environment, it is also a characteristic finding in the lungs of people with cystic fibrosis. It is particularly virulent and associated with a significantly worse prognosis than those people with cystic fibrosis who do not have it chronically.

Levofloxacin inhalation solution (LIS) is an antibiotic manufactured and licensed for use in people with cystic fibrosis. Its antimicrobial properties are targeted against *Pseudomonas aeruginosa*.

4 Aims and Objectives

This policy proposition aims to detail the clinical criteria under which NHS England will routinely fund the inhaled therapy levofloxacin inhalation solution (LIS) for people with cystic fibrosis.

The objectives are to:

- a) Determine which groups of people with cystic fibrosis may benefit from the use of LIS

- b) Determine in what circumstances use of LIS should be approved
- c) Determine the use of LIS in respect to other inhaled antibiotic approved for use in people with cystic fibrosis by NHS England, as laid out in the Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf>

5 Epidemiology and Needs Assessment

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting around 8,823 people in England. It affects all mucus producing cells resulting in dehydrated secretions throughout the body, particularly damaging to the lungs, the gut and the pancreas. These secretions become thick and block the airways and the flow of digestive juices in the gut. As a result, patients get recurrent and long-term infections in the lungs (which are the main cause of morbidity and mortality) and have problems with the digestion and absorption of food resulting in poor growth. Median survival for patients with cystic fibrosis is currently 47 years (UK CF Registry 2015). However, the median age at death is currently 29 years. Most people with cystic fibrosis who die each year are young adults.

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 and more frequent periods in hospital. Severely ill patients may need lung, heart or heart/lung transplants. Annual expenditure on standard care (excluding transplantation) for cystic fibrosis in England is around £100m.

NHS England has a formal clinical commissioning policy to fund inhaled therapies for patients which includes treatment for the commonest and most serious infection: pulmonary *Pseudomonas aeruginosa* infection (A01/P/b). Approximately 50% of people with cystic fibrosis are either chronically or intermittently colonised with Pa (UK National Registry Report 2015) Three antibiotics are funded, in a stepwise approach i.e. colistimethate, tobramycin and aztreonam.

90% of deaths in patients with cystic fibrosis are due to chronic pulmonary infection with associated lung damage and respiratory failure. Inhaled antibiotics are an

essential strategy to treat these infections, and for slowing and preventing the resulting pulmonary damage. The three currently commissioned antibiotics (colistimethate, tobramycin and aztreonam) may be or become unsuitable for some individual patients due to intolerability, microbial resistance or clinical deterioration. Therefore there is a need for new inhaled antibiotics with activity against *Pseudomonas aeruginosa*.

It is estimated that there are around 2400 people in England with cystic fibrosis who are aged 12 years or older **and** who have chronic airways colonisation with *Pseudomonas aeruginosa* (UK CF Registry).

Levofloxacin inhalation solution is licensed for use in people with cystic fibrosis who are chronically colonised with *Pseudomonas aeruginosa* age 18 years and over. Evidence is presented from trials in people with cystic fibrosis from age 12 years and older. However, the NICE Rapid Evidence Review and the NHS England Specialised Commissioning Policy Working Group were concerned about the use of LIS in the 12-17 age group, due to reported significant systemic absorption of LIS and the potential effects on the musculoskeletal-skeletal system when still developing. Thus, those aged less than 18 years are excluded from the scope of this clinical commissioning policy.

The following data relating to England are extracted from The UK National CF Registry by personal communication. The full 2015 registry report is publicly available at www.cysticfibrosis.org.uk. In 2015 the UK National Registry reported 4450 people with cystic fibrosis aged 18 years and over in England. Of these there are 2191 (49%) with chronic *Pseudomonas aeruginosa*. Of these 1965/2191 (90%) were prescribed at least one inhaled antibiotic.

In order to estimate how many people with cystic fibrosis might be prescribed LIS, it is useful to review the uptake of the most recent inhaled antibiotic to be approved for use in people with cystic fibrosis in the UK. Aztreonam lysine became available in 2009, and was approved for use within the policy laid out in the 2012 NHS England Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. Using data captured by the CF National Registry, the increase in use of aztreonam lysine following its approval is as follows (where N is the number of

people with cystic fibrosis age 18 years and older attending Cystic Fibrosis centres in England):

- 2012: $N=89/3536=3\%$
- 2013: $N=271/3816=7\%$
- 2014: $N=527/4057=13\%$
- 2015: $N=602/4450=13.5\%$

It is expected that the future use of LIS by people with cystic fibrosis in England will be no more than that seen for aztreonam lysine, and indeed is likely to be less. This is because the use of LIS is proposed as a fourth line agent, after tobramycin, colistimethate sodium and aztreonam lysine have been tried.

The rationale is that whilst there are no studies comparing aztreonam and levofloxacin, those comparing aztreonam and tobramycin (against which levofloxacin has been compared) showed a much more convincing benefit for aztreonam. In addition, there is significant systemic absorption of levofloxacin, and the quinolones are a class with a wide variety of potential side effects (already recognised in the restriction of the licence to >18yr olds).

6 Evidence Base

It can be difficult to research the use of antipseudomonal drugs in patients with cystic fibrosis.

- It is now common practice to rotate inhaled antibiotics by cycle which means that studies which require administration of repeated cycles of the same product are unlikely to be feasible.
- Very few participants naïve to inhaled antibiotic treatment can be enrolled to studies.
- The age at which chronic colonisation with *Pseudomonas aeruginosa* occurs has generally increased which has impacted on the number of young people who can be recruited to studies.

There are no published studies which directly compare nebulised levofloxacin and

nebulised aztreonam. There are also no published studies comparing nebulised levofloxacin with another inhaled antibiotic in a population of people naïve to both antibiotics.

There are two key studies concerning the efficacy and safety of nebulised levofloxacin for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in people with cystic fibrosis. Flume *et al* (2016) is a double blind randomised controlled trial comparing 28 days of nebulised levofloxacin with placebo. Elborn *et al* (2015) is an open-label randomised non-inferiority study comparing nebulised levofloxacin with nebulised tobramycin over three cycles of treatment.

Flume *et al* (2016)

This study was a multicentre, double-blind, placebo-controlled randomised controlled trial of one cycle of treatment consisting of 28 days treatment and 28 days follow up. The study included 330 patients (55% male) aged over 12 years (mean age 29 years; 85% were aged over 18 years), with a documented diagnosis of cystic fibrosis, a forced expiratory volume in 1 second (FEV1) between 25% and 85% of predicted (mean 56.5%), and a chronic airways infection with *Pseudomonas aeruginosa* (defined as a respiratory secretion culture positive for *Pseudomonas aeruginosa* in the previous 12 months and a positive culture obtained at the screening visit) who had received at least three 28 day courses (or a total of 84 days) of inhaled antibiotics over the previous 12 months, with at least a 14 day course completed within the previous 29 to 84 days.

Patients were randomised 2:1 to either levofloxacin 240 mg nebulised twice daily or 0.9% saline nebulised twice daily. The treatments were blinded for appearance but not taste. Patients continued their usual respiratory care and medications during this study. Antipseudomonal antibiotics other than the study drug were not allowed unless it was deemed necessary to treat a suspected exacerbation by the study investigator.

The primary outcome measure was time to an exacerbation of cystic fibrosis,

defined by concurrently having changes in at least four of the 12 respiratory signs or symptoms that make up the modified Fuchs definition (Fuchs *et al* 1994), or any of the following: early discontinuation from the study, death or treatment with an antipseudomonal antibiotic for an event that did not meet the predefined criteria but was determined to be an exacerbation for the purposes of the primary endpoint by an independent, blinded, exacerbation adjudication committee.

Analysis was by intention to treat.

The median time to first exacerbation was 51.5 days in the levofloxacin group compared to 58.0 days in the placebo group (difference not statistically significant).

The mean change in *Pseudomonas aeruginosa* sputum density (\log_{10} (colony forming units) per gram) was -0.59 in the levofloxacin group compared to 0.04 in the placebo group ($p < 0.05$).

The mean change from baseline to Day 28 in the respiratory domain of the CFQ-R (Cystic Fibrosis Questionnaire Revised) was 4.66 in the levofloxacin group compared to 4.94 in the placebo group (difference not statistically significant).

3.2% of patients in the levofloxacin group reported serious adverse events, compared to none in the placebo group. 4/219 patients in the levofloxacin group withdrew from the study, compared to 1/110 in the placebo group.

Elborn *et al.* 2015

This study was a multicentre open-label comparator randomised trial of three cycles of treatment with each cycle consisting of 28 days treatment and 28 days follow up. Participants and study co-ordinators were aware of the treatment assignment but the site investigators and medical monitors remained blinded.

The study involved 282 patients (57% male) aged 12 years or over (mean age 28 years; 86% were over 18 years) with a documented diagnosis of cystic fibrosis, a forced expiratory volume in 1 second (known as FEV1) between 25% and 85%

predicted (mean 54%), and a chronic airways infection with *Pseudomonas aeruginosa* who had received at least three 28 day courses (or a total of 84 days) of inhaled tobramycin over the previous 12 months, with at least a 14 day course completed within the previous 29 to 56 days. Chronic *Pseudomonas aeruginosa* infection was defined as a respiratory secretion culture positive for *Pseudomonas aeruginosa* in the previous 12 months and a positive culture obtained at the screening visit.

Participants were randomised 2:1 to either levofloxacin 240 mg nebulised twice a day or tobramycin 300 mg nebulised twice daily. Participants were able to continue their routine respiratory care and medications during the study. Antipseudomonal antibiotics other than the study drug were not allowed unless it was deemed necessary to treat a suspected exacerbation by the study investigator.

The primary efficacy outcome was the relative change in FEV1 percentage predicted from baseline to Day 28. The study was designed to show the non-inferiority of nebulised levofloxacin to nebulised tobramycin for the primary outcome with a pre-specified non-inferiority margin of a lower 95% confidence interval greater than -4%. If non-inferiority was demonstrated then a subsequent test for superiority of levofloxacin was to be conducted.

Analysis was by intention to treat.

The percentage predicted FEV1 in the levofloxacin group was 54.8% at baseline and 56.0% at Day 28. This compared to the tobramycin group where it was 52.2% at baseline and 53.3% at Day 28. The mean relative change was not statistically significant ie levofloxacin was non-inferior to tobramycin but not superior.

Median time to first exacerbation was 131 days in the levofloxacin group compared to 90.5 days in the tobramycin group (difference not statistically significant).

Median time to administration of antipseudomonal antibiotics other than the study drug was 141 days in the levofloxacin group compared to 110 days in the tobramycin group ($p=0.04$).

Median change in *Pseudomonas aeruginosa* sputum density (\log_{10} CFUs per gram) in the levofloxacin group was -0.51 from baseline to Day 28, and -0.13 from baseline to Day 168. In the tobramycin group the median change in sputum density was -0.87 from baseline to Day 28 and -0.25 from baseline to Day 168 (difference between the two drugs not statistically significant).

22.0% of patients treated with levofloxacin and 32.2% of patients treated with tobramycin reported serious adverse events.

Levofloxacin nebuliser solution is not licensed for use in children and young people aged less than 18 years. The manufacturers had originally submitted a license application which included children and young people from the age of 12 and 30 kg body weight. However, due to safety concerns the manufacturer withdrew the license application for children and young people under 18. Further safety studies including safety studies in children and young people under 18 are planned.

The European Public Assessment Report (EPAR) for levofloxacin reported that serum concentrations of levofloxacin from nebulised administration were on average approximately 50% of that seen with oral and intravenous routes of administration (at a dose of 500 mg daily). Therefore all of the possible adverse effects associated with oral or intravenous administration of levofloxacin (with the exception of those specific to the route of administration) are also a potential risk with the nebulised formulation. This is reflected in the summary of product characteristics which includes warnings and precautions for use associated with systemic administration of levofloxacin and the fluoroquinolone class of antibiotics, as well as those specific for inhaled administration (such as bronchospasm).

7 Proposed Criteria for Commissioning

Treatment with levofloxacin inhalation solution will be routinely funded in the circumstances outlined below. This guidance should be read in conjunction with the NHS England Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. This guidance applies to adults only. LIS is effective

for the treatment of chronic pulmonary *Pseudomonas aeruginosa* infection for people with cystic fibrosis age 18 and older. However other therapies are available for the same indication which have greater evidence of efficacy, and have evidence of less systemic absorption and less risk of side effects.

- Treatment with LIS should only be initiated by a specialist cystic fibrosis centre.
- Treatment with LIS should only be initiated in adults aged 18 and over with evidence of chronic *Pseudomonas aeruginosa* infection - commonly accepted as at least half the samples taken in the previous twelve months culture positive for *Pseudomonas aeruginosa*.
- Treatment with LIS should only be initiated after demonstrable treatment failure with an alternative inhaled antibiotic in the stepwise approach outlined in the NHS England Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis.
- LIS should be considered a fourth line therapy after colistimethate sodium, tobramycin, and aztreonam lysine.
- Reasons for deeming treatment failure with other inhaled antibiotics include: continued accelerated decline in lung function (greater than 2% per year decline in FEV1 as percent of predicted); continued excessive i.e. more than two exacerbations requiring rescue intravenous antibiotics in a year; intolerance or allergy to alternative inhaled antibiotics.
- The licensed dosing schedule of “alternating cycles of 28 days on treatment followed by 28 days off treatment” should be employed.
- This may be prescribed either alternating with colistin or tobramycin or aztreonam lysine depending on the clinical response to those medications previously.

Contraindications:

- Known allergy to levofloxacin or to other quinolone antibiotic (moxifloxacin, ciprofloxacin, ofloxacin).
- Previously suffering with tendonitis or tendon rupture associated with the use of a quinolone antibiotic.
- Epilepsy.

- Pregnancy.

8 Proposed Patient Pathway

This pathway is only for patients aged 18 years and over. However the NHS England Clinical Commissioning Policy for Inhaled Therapy for Adults and Children with Cystic Fibrosis (A01/P/b; 2015) remains valid. The policy states:

- All patients should be prescribed a supervised test dose of a new inhaled antibiotic in the hospital environment before commencing therapy. An inhaled or nebulised bronchodilator should be administered before the test dose if this is part of the patient's current regimen. The test dose should be supervised by a nurse, physiotherapist or lung function technician and the patient should have pre and post dose FEV1 and FVC measured. The patient should also be monitored for post-dose wheezing and bronchoconstriction.
- The test dose may be repeated at least 24 hours later if wheezing or bronchoconstriction occurs, after the administration of nebulised bronchodilator (if not administered before the first test dose). If the patient tolerates the repeated test dose, they should use nebulised bronchodilator before each subsequent dose.
- All patients should have regular review of sputum microbiology to ensure continued appropriate ongoing treatment. If *Pseudomonas aeruginosa* has not been isolated or has been replaced by a new organism (i.e. *Burkholderia cepacia*) then a change of therapy should be considered.
- All patients should have a regular assessment of lung function to ensure ongoing treatment tolerance and identification of adverse effects. If there is evidence of bronchoconstriction associated with ongoing therapy, then the inhaled antibiotic should be discontinued and an alternative tried.
- Due to the significant systemic absorption of LIS interactions with other medications should be monitored.

9 Proposed Governance Arrangements

See NHS England National Service Specification: Cystic Fibrosis (adults) A01/S/a ().

Available from <https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-a/a01/>.

10 Proposed Mechanism for Funding

Named inhaled therapies (as detailed in this policy) are medicines that are excluded from the national year-of-care cystic fibrosis tariff. They are funded by pass through payments made against invoices raised by provider Trusts.

11 Proposed Audit Requirements

Services will meet the minimum dataset requirements of the UK CF Registry as detailed in the cystic fibrosis service specifications.

12 Documents That Have Informed This Policy Proposition

NHS England Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis Reference A01/P/b (2015). Available from <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf> [accessed 3rd November 2016].

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13 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.

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registry/full-registry-report-2015.ashx?la=en](https://www.cysticfibrosis.org.uk/~media/documents/the-work-we-do/uk-cf-registry/full-registry-report-2015.ashx?la=en) [accessed 3rd November 2016]

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