



Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis

Reference: NHS England A01/P/b

NHS England

Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis

First published: December 2014

Prepared by NHS England Clinical Reference Group for Cystic Fibrosis

Published by NHS England, in electronic format only.

NHS England INFORMATION READER BOX**Directorate**

Medical	Commissioning Operations	Patients and Information
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference: 02654

Document Purpose	Policy
Document Name	Clinical Commissioning Policy for Inhaled Therapies for Adults and Children with Cystic Fibrosis
Author	NHS England
Publication Date	January 2015
Target Audience	CCG Clinical Leaders, CCG Accountable Officers, CSU Managing Directors, Care Trust CEs, Foundation Trust CEs, Medical Directors, Directors of PH, NHS England Regional Directors, NHS England Area Directors, Special HA CEs, GPs, NHS Trust CEs
Additional Circulation List	
Description	This policy aims to detail the clinical criteria under which NHS England will routinely fund inhaled therapies (namely Aztreonam lysine, Colistimethate sodium, Dornase alpha, Tobramycin and Mannitol) for people with Cystic Fibrosis
Cross Reference	N/A
Superseded Docs (if applicable)	N/A
Action Required	N/A
Timing / Deadlines (if applicable)	
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Document Status

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Policy Statement

NHS England will commission inhaled therapies for people with Cystic Fibrosis in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Throughout the production of this document, due regard has been given 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 in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Cystic fibrosis (CF) is the most common, life-limiting, inherited disease in the UK. It affects about 7,700 people in England.

Cystic Fibrosis is caused by a single faulty gene that controls the movement of salt in the body. In people with CF, 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 CF can also have other problems including diabetes, infertility and osteoporosis.

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.

1. Introduction

<p>Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting about 9,000 people (7,700 in England). It affects the cells that</p>
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secrete mucus in the lungs and the cells that secrete digestive juices from the glands in the gut and pancreas. These secretions become thick and block the airways and the flow of digestive juices in the gut. As a result, patients get long-term infection and inflammation 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 41.4 years (CF Registry 2010). However, the median age at death is currently 27 years. Most people with CF who die each year are young adults.

Current treatments aim to treat the symptoms of cystic fibrosis and include:

- Regular, frequent chest physiotherapy
- Specialist dietary advice, supplements and enzyme replacement therapy

Medicines (many of them high-cost) to relieve bronchospasm and inflammation in the lungs, reduce the viscosity of mucus in the airways or treat serious infection in the lungs.

In April 2012 a national commissioning policy was agreed by the 10 Specialised Commissioning Groups (SCGs) in England. This policy detailed the circumstances in which four named medicines (Aztreonam lysine, Colistimethate sodium, Dornase alpha and Tobramycin) to treat cystic fibrosis would be routinely funded. The policy specifically addressed the nebulised forms of these drugs. The policy was subsequently adopted as clinical commissioning policy statement A01/PS/a by NHS England.

Some of these treatments are now available in dry powder form. The National Institute for Health and Clinical Excellence (NICE) has issued guidance on the dry powder forms of Colistimethate sodium and Tobramycin in March 2013 (TAG no.276) and inhaled Mannitol, an osmotic mucolytic, in November 2012 (TAG no.266).

NHS England has updated the clinical commissioning criteria in line with NICE guidance and expanded the policy statement into a full clinical commissioning policy.

2. Definitions

See Introduction.

3. Aim and objectives

This policy aims to detail the clinical criteria under which NS England will routinely fund inhaled therapies (namely Aztreonam lysine, Colistimethate sodium, Dornase alpha, Tobramycin and Mannitol) for people with Cystic Fibrosis.

4. Epidemiology and needs assessment

Cystic Fibrosis (CF) is the most common, life-threatening, autosomal recessive disorder in Caucasian populations; it has an estimated carrier rate of 1 in 25 and

incidence of 1 in 2,500 live births. It affects around 9,000 people in the UK with a prevalence of 1.37/10,000.

CF was first recognised as a distinct disease in 1938. It is characterised by abnormal transport of chloride and sodium, leading to thick viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract and to an increased salt content in sweat gland secretions.

Most of the morbidity and mortality is from pulmonary disease, which is characterised by bronchial and bronchiolar obstruction with thick tenacious secretions that are difficult to clear, colonisation by pathogenic bacteria and repeated infections. There is chronic inflammation and progressive lung destruction can lead to bronchiectasis, altered pulmonary function, and respiratory failure.

CF can also lead to CF related diabetes (CFRD), male infertility and liver involvement. In addition to repeated chest infections, symptoms of CF can include a troublesome cough, prolonged diarrhoea and poor weight gain.

Most patients with CF eventually succumb to lung disease and life expectancy of patients with CF is currently around 30 years, a considerable increase from around six months when the disease was first identified, and is expected to increase to at least 50 years for children born in 2000.

There is no cure for CF and current treatments generally target the complications rather than cause of the disease. Treatments can be broadly classified as nutritional repletion (e.g. pancreatic enzyme supplementation and nutritional supplementation), relief of airway obstruction (e.g. physiotherapy, drugs to improve sputum clearance, bronchodilators), treatment of airway infection (e.g. antibiotics), suppression of inflammation (e.g. steroids, high dose ibuprofen) and lung transplantation.

5. Evidence base

All treatments covered by this policy (with the exception of nebulized Aztreonam lysine and Dornase alpha) have been evidence reviewed by the National Institute for Health and Care Excellence (NICE) in the following Technology Appraisal Guidance (TAG) documents:

[NICE Technology Appraisal Guidance no. 266](#)

[NICE Technology Appraisal Guidance no.276](#)

Nebulised aztreonam was reviewed by the All Wales Medicines Strategy Group in 2012 (<http://www.awmsg.org/awmsgonline/app/appraisalinfo/1715>).

6. Rationale behind the policy statement

There is good evidence that inhaled therapies are both clinically and cost effective (see NICE TAG 266 and 276). However the NICE appraisals do not detail how individual medicines should be used clinically in relation to each other. This policy provides detailed guidance on the drug regimen that will provide the greatest clinical and cost effective use of these products.

This approach has been recommended by the Cystic Fibrosis Clinical Reference

Group, which provides clinical advice to NHS England.

7. Criteria for commissioning

National Commissioning Criteria for Inhaled Treatments for Cystic Fibrosis

1. Approved treatments

1.1. Treatment with the following inhaled treatments will be routinely funded for adults and children with a confirmed diagnosis of cystic fibrosis (CF) who meet clinical criteria for their use.

NB Treatments are typically not licensed for use in children under the age of 6 years, but such use is commonplace and clinically appropriate and, therefore, included in this policy.

Antibiotics:

- Aztreonam lysine (brand Cayston)
- Colistimethate sodium (brands Collmycin, Promixin, Colobreathe)
- Tobramycin (brands Tobi, Tobi Podhaler, Bramitob)

Mucoactive drugs:

- Dornase alpha (brand Pulmozyme) (mucolytic agent)
- Mannitol (brand Bronchitol) (hyposmolar agent)

1.2. Treatment should be initiated and, where appropriate, escalated with the least expensive suitable product.

1.3. Treatment should only be initiated by a specialist cystic fibrosis centre. Continued supplies of a treatment may be prescribed by the specialist centre, by the network clinic in agreement with the specialist centre, or by the patient's GP in accordance with a shared-care agreement unless a patient access scheme would preclude this. However, during 2014-2016 it is the intention of NHS England to confine prescribing of these drugs to secondary care. Changes to prescribing will be via a managed process involving patients and their families, specialist CF providers and Clinical Commissioning Groups. From April 2016 these treatments will only be prescribed by secondary care.

1.4. Products that are available for administration by dry powder inhaler are available as an option if they are prescribed in line with NICE guidance and the guidance contained in this document.

2. Eradication of *Pseudomonas aeruginosa*

2.1. Preventing chronic infection with *Pseudomonas aeruginosa* is a key element in increasing survival in patients with CF.

2.2. Therapy with Colistimethate sodium for 3 months or Tobramycin for one to three months (in combination with oral ciprofloxacin) is used.

2.3. A test dose should be administered as described below and therapy continued, with a review of sputum microbiology, until confirmed eradication of *Pseudomonas aeruginosa*.

2.4. Eradication therapy may be repeated if previous attempts were successful.

3. Treating chronic *Pseudomonas aeruginosa* infection

3.1. It is recommended that all patients with evidence of chronic *Pseudomonas* infection should receive therapy with nebulised/inhaled anti-*Pseudomonas* antibiotic.

3.2. In some patients, adherence to treatment may be improved if prescribed as a month on/month off treatment regimen of inhaled Tobramycin twice daily before being able to maintain a chronic daily regimen.

3.3. Trials to establish the best regimen have not been conducted, but in Europe it is accepted best practice to prescribe a continuous daily suppressive regimen. It is an option if clinically indicated.

3.4. A test dose should be administered and patients monitored as described below.

3.5. A stepwise approach is recommended:

3.5.1. Colistimethate sodium is used first line when pulmonary function is normal but chronic *Pseudomonas* infection is evident. As per NICE guidance, Colistimethate sodium dry powder inhaler can be used for patients who have previously been prescribed Colistimethate sodium nebulised treatment and would continue to benefit from treatment but have otherwise become intolerant or have struggled to adhere with nebulised treatment and therefore would be switched to a more expensive product such as Tobramycin nebules.

In the same way that different nebulised antibiotics can be given as a continuous daily suppressive regime on a month on/month off basis, different dry powder inhalers can be used in an alternate monthly regimen with other inhalers or nebulised treatments. E.g. Tobi Podhaler alternated each month with Colobreathe inhaler, Tobi Podhaler alternated with Aztreonam lysine nebules.

3.5.2. Tobramycin should be considered if, despite continued therapy and good adherence to treatment, lung function continues to decline or there is a requirement for more than one course of IV antibiotics in the preceding year. This may be prescribed alternate months in conjunction with Colistimethate sodium.

3.5.3. Aztreonam lysine may be considered if there is still progressive loss of lung function (defined as greater than 2% per year decline in FEV1 as % of predicted) or there is continued need for IV therapy for exacerbations i.e. more than 2 per year despite therapy with an alternating regimen of

Tobramycin and colistin. This may be prescribed either alternating with colistin or Tobramycin depending on the clinical response to those medications previously.

3.6. Treatment choice is determined by clinical response. Failed eradication or pseudomonal regrowth whilst on inhaled antibiotics may necessitate a change in antibiotic.

3.7. In the event of intolerance/allergy to an antibiotic e.g. Colistimethate sodium, then an alternative should be tried. Tobramycin should be regarded as second line therapy and Aztreonam lysine as third line.

4. Test Dose

4.1. All patients should be prescribed a supervised test dose in the hospital environment before commencing therapy. A 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.

4.2. 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.

5. Monitoring

5.1. All patients should have regular review of sputum microbiology to ensure continued appropriate ongoing treatment. If Pseudomonas has not been isolated or has been replaced by a new organism (i.e. Burkholderia cepacia) then a change of therapy should be considered.

5.2. 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.

5.3. Colistimethate sodium has not been shown to improve lung function in studies therefore if there is continued loss of lung function (more than 1% per year) alternative antibiotics should be considered.

5.4. The aim of therapy in children is to maintain lung function in the normal range i.e. greater than 85% predicted and in adults to maintain lung function at levels at transition.

5.5. Specific monitoring for Tobramycin - As small amounts of drug are absorbed from the lung into the systemic circulation there is a potential for patients

with pre-existing renal disease or those with pre-existing high cumulative doses of systemic Tobramycin to suffer ototoxicity. The CF team should make patients aware of potential side effects such as ringing in the ears and ensure therapy is stopped if this occurs. At risk patients may require baseline audiometry when starting therapy.

6. Mucoactive drugs

- 6.1. Dornase alpha is used in children aged 6 and above to prevent mucus plugging and deterioration in lung function. It may be prescribed in younger children with persistent cough relating to mucus plugging in accordance with European guidelines (JCF 2009; 295-315) in order to prevent decline and reduce the requirement for IV therapy for exacerbations.
- 6.2. The effect of Dornase alpha is independent of sputum bacteriology.
- 6.3. Patients must be able to perform adequate airway clearance following Dornase alpha and should not receive this therapy unless airway clearance techniques are adequate.
- 6.4. All patients should be prescribed a supervised test dose before commencing therapy. 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.
- 6.5. FEV₁ and FVC should be measured before and after a trial period of 14 to 28 days.
- 6.6. Treatment with Dornase alpha should be discontinued in patients whose lung function has deteriorated after the trial period. A longer trial period (up to 3 months) may be warranted in some cases where there is severe disease.
- 6.7. Patients who discontinue Dornase alpha may be considered for a repeat trial in the future.
- 6.8. Mannitol dry powder inhaler (Bronchitol) is a mucoactive hyperosmolar agent that causes water to enter the airway lumen and hydrate airway secretions. This reduces the viscosity of secretions and stimulates cough, thereby increasing the clearance of secretions and pathogenic bacteria. The evidence for its use and the circumstances in which it can be prescribed is outlined in the NICE guidance. To summarise this here, Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:
 - who cannot use rhDNase because of ineligibility, intolerance or who have an inadequate response to rhDNase
and
 - whose lung function is rapidly declining (forced expiratory volume in 1 second [FEV₁] decline greater than 2% annually)
and

- for whom other osmotic agents are not considered appropriate.

8. Patient pathway

Inhaled therapies for people with Cystic Fibrosis may be considered as an option in line with the criteria detailed in section 7 of this policy.

9. Governance arrangements

See national service specification for cystic fibrosis services.

10. 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.

Tobramycin dry powder for inhalation is supplied by a preferentially priced patient access scheme (PAS) to be delivered through secondary care initiated homecare. As such GP shared care prescribing of this product is not supported.

Colistimethate sodium dry powder for inhalation is supplied by a preferentially priced PAS. It is recommended that the prescription and homecare initiation be limited to specialist care for monitoring, tracking and reimbursement.

Mannitol dry powder inhaler has a flat rate of discount across all sectors but its prescription should be limited to specialist care.

11. Audit requirements

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

12. Documents which have informed this policy

[NICE Technology Appraisal Guidance no. 266](#)

[NICE Technology Appraisal Guidance no.276](#)

All Wales Medicines Strategy Group review of nebulised Aztreonam lysine (<http://www.awmsg.org/awmsgonline/app/appraisalinfo/1715>).

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in April 2016 unless information is received which

indicates that the proposed review date should be brought forward or delayed.