

**Clinical  
Commissioning  
Policy: Ivacaftor for  
children aged 2-5  
years with cystic  
fibrosis (named  
mutations)**

Reference: NHS England: 16049/P



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# **Clinical Commissioning Policy: Ivacaftor for children aged 2-5 years with cystic fibrosis (named mutations)**

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**Prepared by NHS England Specialised Services Clinical Reference Group for Cystic Fibrosis**

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## **Policy Statement**

NHS England will commission ivacaftor for children aged 2 to 5 years with cystic fibrosis (named mutations) 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**

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 an inherited disease, caused by a faulty gene. This gene controls movement of salt and water in and out of cells. This means the lungs and digestive system become clogged with mucus – making it hard to breathe and digest food.

- CF is the most common, life-limiting, inherited disease in the United Kingdom (UK).
- Most cases are now diagnosed soon after birth.
- Around one in 25 of the population carry the faulty gene.

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When people with CF have a build-up of mucus in the lungs it can make it difficult to clear the airway.

- This creates conditions in which bacteria can grow easily and well.
- Some of these bacteria can cause lung infections which keep coming back – these infections then damage the airways.
- This makes patient's less able to breathe freely – this seriously affects their quality of life.

### **About current treatments**

Current treatments for CF treat the symptoms of CF, such as chest infections.

### **About the new treatment**

Ivacaftor is a new medicine that works differently.

- It works by targeting the faulty gene (CFTR) and correcting its function.
- This reduces the amount of mucus that is produced.
- This reduces many of the problems you get with CF.

Ivacaftor is currently used routinely for all CF patients who:

- are aged 6 years and older.
- have one of the following nine gene mutations: G551D, G178R, S549N, S459R, G551S, G1244E, S1251N, S1255P or G1349D. (Clinical Commissioning Policy: Ivacaftor for cystic fibrosis (named mutations) A01/P/a).

### **What we have decided**

NHS England has carefully reviewed the evidence to treat children with cystic fibrosis (aged 2 to 5 years and with one of the above named mutations) with ivacaftor. We have concluded that there is enough evidence to consider making the treatment available. Whilst the evidence in the 2 to 5 years age group is limited, it is recognised that there is high quality evidence in children aged 6 years and older.

## 1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a policy to routinely commission ivacaftor for children aged 2-5 years with cystic fibrosis.

Cystic fibrosis is the most common, life-limiting, recessively inherited disease in the UK, affecting approximately 10,500 people. The underlying problem is a mutation in a gene that encodes for a chloride channel CFTR. This is essential for the regulation of salt and water movements across cell membranes. Absent or reduced function of CFTR results in dehydration of secretions leading to problems with mucus clearance, resulting in damage to the lungs, gut and pancreas. Impaired functioning of this protein may be due to a number of mutations, the most common being the  $\Delta F508$  mutation, which occurs in around 88% of patients with cystic fibrosis in the UK, whereas the G551D mutation occurs in around 6%.

Current standard treatments for CF aim to treat the symptoms of cystic fibrosis but do not treat the underlying cause. Ivacaftor is the first in a new class of medicines (CFTR potentiators) that target CFTR and so treat the underlying cause of the disease.

Ivacaftor was designated as an orphan medicine in the EU in 2008. In July 2012, it received EU marketing authorisation for the “treatment of cystic fibrosis in patients aged six years and above who have the G551D mutation in their gene for the protein called cystic fibrosis transmembrane conductance regulator (CFTR)”. This approval was extended in 2014 to cover a further 8 mutations. On 18th November 2015, the license was expanded again to include use of the granule formulation in children aged 2 years and older with the named mutations.

NHS England routinely commissions ivacaftor for patients with a diagnosis of cystic fibrosis and at least one copy of one of the nine specified gene mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D) and who are aged 6 years or over (Clinical Commissioning Policy: Ivacaftor for cystic fibrosis (named mutations) A01/P/a, first published January 2013 and updated July 2015).

## 2 Definitions

Cystic fibrosis (CF) is an inherited disease that affects all mucus producing cells resulting in dehydrated secretions throughout the body, particularly damaging 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 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.

Ivacaftor is a drug that treats the underlying cause of CF by improving the transport of salt and water across cell membranes, which helps hydrate and clear mucus.

Sweat chloride test measures the concentration of salt in a person's sweat. A high salt level indicates CF.

Alleles are alternative forms of the same gene, i.e. the gene at the same locus (position on a chromosome).

The medicine is now available as 'granules' than can be mixed with food. The granules have been shown to be safe in 2 to 5 year olds. They have also been shown to have the same effect as other forms of the medicine. Ivacaftor has also just been licensed by the European Medicines Agency (EMA) in this age group.

## 3 Aims and Objectives

This policy aims to define NHS England's commissioning position on ivacaftor as part of the treatment pathway for children aged 2-5 years with cystic fibrosis.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for children aged 2-5 years with cystic fibrosis.

## 4 Epidemiology and Needs Assessment

Cystic fibrosis is the most common, life-limiting, recessively inherited disease in the UK, affecting approximately 10,500 people (2014 data from UK CF Registry 2015). 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. Cystic fibrosis causes damage from birth and 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 (NHSE policy A01/P/a). Median predicted survival for patients with cystic fibrosis is currently 40.1 years, i.e. half of the people with cystic fibrosis are predicted to live at least 40.1 years; however the median age of death of the 137 people who died in 2014 was 28 years (2014 data from UK CF Registry 2015).

CF is caused by mutations in the CFTR gene which was discovered in 1989. It is estimated that there are around 1,100 children aged between 2 and 5 years (up to their 6th birthday) with cystic fibrosis, of whom around 45 in the England will have one of the specified gating mutations: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D (UK CF Registry 2015).

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

NHS England has concluded that there is sufficient evidence to support routine commissioning of ivacaftor for children aged 2-5 years with cystic fibrosis. Whilst the evidence in this age group is limited, there is a strong rationale for commissioning ivacaftor in 2-5 year olds for the following reasons:

- NHS England has routinely commissioned this drug in children aged 6 and over since 2013 and good (level 1) evidence for the effectiveness of ivacaftor in children over 6 years old
- The EMA has recently expanded the license for ivacaftor for use in this age group, with a granule formulation
- The safety profile and pharmacokinetics have shown to be similar in children aged 2-5 years
- There was a highly significant fall in sweat chloride concentrations in children aged 2-5 years treated with the new drug formulation
- Clinical expertise agrees that intervening early in CF and preventing CF-induced damage improves life expectancy, and may improve cost effectiveness by reducing future complications
- An RCT would be difficult to perform on these patient numbers (66 in the UK); therefore level 1 evidence is unlikely to become available in this population

### **Is ivacaftor clinically effective in children aged 2-5 years who have cystic fibrosis with the specified gating mutations?**

There is relatively limited evidence that is specific to children in the age group 2-5 years who have CF with one of the specified gating mutations. To date there are no RCTs in this population. However, there is high grade evidence (level -1/1) supporting the use of ivacaftor 150mg twice a day in children who have CF and the nine named gating mutations who were aged greater than 6 years. In this older paediatric population, four RCTs have evaluated and measured the following outcomes:

- Changes in lung function

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- Changes in nutritional status
- Changes in sweat chloride concentration.

The results of all four RCTs show a statistical significance; increase in FEV1 ( $P < 0.001$ ), decrease in sweat chloride concentration ( $P < 0.0001$ ) and increase in weight ( $P = 0.0004$ ) in patients receiving treatment with ivacaftor 150mg twice a day at 48 weeks. A double blind study (Davies et al, 2013) in which the mean paediatric age was 8.9 years of age also showed an improvement in lung function 12% of predicted FEV1 compared with standard care at 24 weeks were measured. There was weight gain of 2.7kg at 48 weeks and a decrease in sweat chloride concentration (treatment effect -54.3mmol/L) which was greatest on day 15. An additional RCT looked at ivacaftor 150mg in patients  $\geq 6$  years old with CF and non-G551D gating mutations (G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D). This also confirmed positive impacts on main outcomes including FEV1 and sweat chloride, indicating benefit for both the main clinical and biochemical outcomes.

As ivacaftor has been licensed since 2012 for children aged 6 and over, new RCT evidence is not expected. However, there is some recent evidence (level 2-) indicating that the rate of decline of lung function was slowed by half over a 3 year period in the treatment group when matched with up to 5 homozygous F508del control patients, not eligible to receive ivacaftor (Sawicki et al, 2015).

The formal evidence level to support the use of ivacaftor directly in children aged 2-5 years who have CF with a specified gating mutation is low (grade 3). This comes from a phase III open label study (Davies et al, 2015) undertaken to determine safety and confirm pharmacokinetics/pharmacodynamics in this age group. It confirmed that improvements in sweat chloride concentration ( $-46.9 \pm 26.2$  mmol/L,  $P < 0.0001$ ), weight ( $0.2 \pm 0.3$ ,  $P < 0.0001$ ) and faecal elastase ( $99.8 \pm 138.5$ ug/g) were seen at 24 weeks, consistent with positive outcomes seen in the above RCTs and indicating that extrapolation of the results from older children is biologically plausible. As the drug is now licensed for both US and European patients aged 2 and above, new RCTs are unlikely.

Patients treated with the ivacaftor granules showed improvement in their 'nutritional status' - this shows that problems with digesting food may have been reduced.

The evidence to date suggests most adverse events encountered by patients following treatment with ivacaftor were no more frequent than those in the placebo group. Most frequent mild adverse events noted were cough, headaches, dizziness and pulmonary exacerbations. Non-congenital lens opacities (cataracts), without impairment of vision, have been reported in children <12 years old treated with ivacaftor. Causality is not proven but an association cannot be excluded.

### **Is ivacaftor cost effective in children aged 2-5 years who have cystic fibrosis with the specified gating mutations?**

There is sparse evidence on the cost effectiveness of ivacaftor. A systematic review (Whiting et al, 2014) showed the incremental cost effectiveness ratio (ICER) for ivacaftor varied between £335,000 and £1,274,000 per Quality Adjusted Life Year (QALY). The total additional lifetime cost for all eligible CF patients in England ranged from £438 million to £479 million for the lifetime cost and for standard care the lifetime cost was £72 million.

## **6 Criteria for Commissioning**

### **Initiation:**

Ivacaftor will be routinely commissioned for all children aged 2-5 years with cystic fibrosis and at least one copy of one of the following gene mutations: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P or G1349D. Ivacaftor will only be prescribed by a specialist centre.

All patients must have had a sweat chloride test and faecal pancreatic elastase-1 within the six months prior to starting treatment and be informed of the stopping criteria at the time of starting treatment with ivacaftor.

Baseline liver function should be recorded (Transaminases; ALT or AST). Dose modification may be required in patients with hepatic impairment as detailed in the manufacturer's prescribing information. There is no experience of the use of ivacaftor

in patients with severe hepatic impairment and therefore its use is not recommended unless the benefits outweigh the risks.

An ophthalmic examination should be recorded before starting treatment.

**Monitoring:**

The overall clinical assessment of response is as important as any change in biomarkers such as sweat chloride and faecal elastase-1.

After starting ivacaftor, the sweat chloride test will be repeated at the next routine appointment to determine whether sweat chloride levels have reduced, typically by between 20 and 70mmol/l. The sweat chloride level will then be re-checked six months after starting treatment and annually thereafter to confirm sustained reduction. If the sweat chloride levels do not reduce, the patient's clinician will first explore any problems in following the recommended dosing schedule for ivacaftor and its administration with a fat containing snack. The patient's sweat chloride will then be re-tested.

Nutritional status will be monitored at all follow-up appointments and at 6 months a repeat faecal elastase-1 should be checked to review pancreatic function.

Unlike older children and adults, 2-5 year olds are too young to perform pulmonary function tests in routine clinical practice and so these cannot be used to assess treatment outcomes in this age group.

Liver function (Transaminases; ALT or AST) should be assessed every 3 months during the first year of treatment and annually thereafter. In patients with a history of transaminase elevations, more frequent monitoring should be considered and changes closely monitored until they resolve. Dosing should be interrupted in patients with transaminase levels greater than 5 times the upper limit of normal and after resolution, consider the benefits and risks before resuming ivacaftor treatment.

Annual follow-up ophthalmic examinations should be considered in children <12 years.

The manufacturer's prescribing information details interactions with drugs that inhibit or induce CYP3A metabolism. Concomitant medications should be reviewed and treatment or dose modifications made accordingly.

**Stopping criteria:**

If there is a lack of a clinical response as judged by clinical experts and a failure of sweat chloride to reduce then ivacaftor should be stopped.

Allergy to ivacaftor (rashes are usually transient).

Non-adherence (for which safeguarding should be considered).

Significant liver function abnormalities (above).

**Exclusion criteria:**

Hypersensitivity to ivacaftor.

## 7 Patient Pathway

Cystic fibrosis can be diagnosed through the sweat test, newborn screening or genetic testing. The sweat test detects elevated levels of chloride in sweat with a diagnosis of CF being made at levels above 60mmol/L, and a possible diagnosis of CF at levels above 30mmol/L. Newborn screening tests have been introduced in many countries, and have been routine throughout the UK since October 2007. These involve a small sample of blood being taken ("heel prick test") which is tested for high levels of immunoreactive trypsinogen (IRT). If an abnormal IRT value is identified, most new born screening programmes perform a combination of DNA testing to identify known CFTR mutations and repeat IRT testing. IRT testing alone has a sensitivity of 82-100%, double IRT testing increases sensitivity to 89-100% and IRT and DNA testing has a sensitivity of 94-100%; specificity is >99% for all testing strategies. In the UK screening programme, the initial DNA test involves testing for four mutations ( $\Delta F508$ , G551D, G542X and 621+1G>T), if only one CF mutation is detected then further DNA analysis based on 29 or 31 mutations is recommended. The diagnosis is then confirmed using the sweat test.

Ivacaftor will be added to existing standard treatment. Treatment will continue unless the patient meets stopping criteria. Ivacaftor will only be prescribed by a specialist centre. It is not suitable for shared-care prescribing by the patient's GP.

Ivacaftor is immediate-release dosage form of oral administration. In line with the recent marketing authorisation, each sachet, equivalent to one unit dose of 50mg or 75mg of ivacaftor granules q12h (dose based on weight), is mixed with one teaspoon of protocol-approved soft food and administered orally with fat-containing food.

## **8 Governance Arrangements**

See National Service Specification for Cystic Fibrosis (Children) A01/S/b.

## **9 Mechanism for Funding**

Ivacaftor is a high cost drug excluded from PbR tariff. It will be funded through pass through payment against invoices received from provider Trusts.

## **10 Audit Requirements**

New patients will need to be notified through prior notification.

Outcomes must be reported in the CF registry.

Specific audit reports on the use of ivacaftor and specific outcomes in this age group will be requested by the commissioner. Participation in research studies is encouraged.

## **11 Documents which have informed this Policy**

Clinical Commissioning Policy: Ivacaftor for cystic fibrosis (named mutations)  
A01/P/a

## **12 Date of Review**

This document will be reviewed when information is received which indicates that the policy requires revision.

## References

UK CF Registry 2015

<https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry>

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