



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

**Reference: NHS England A01X01/01**

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

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## Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

## Plain Language Summary

The policy proposition aims to confirm NHS England's commissioning approach to ivacaftor for children aged 2-5 years old with cystic fibrosis.

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 into the gut. People with cystic fibrosis can also have other problems including diabetes, infertility, and osteoporosis.

Current treatments for cystic fibrosis treat the symptoms of cystic fibrosis, such as chest infections. Ivacaftor is a new medicine that works differently by targeting the faulty gene product (CFTR) and correcting its function, consequently reducing the production of the thick sticky mucus that causes many of the problems. Ivacaftor is currently routinely commissioned for all patients aged 6 years and older with cystic fibrosis who 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).

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of ivacaftor for children aged 2-5 years old with cystic fibrosis and the above named mutations. Whilst the evidence in this age group is limited, it is recognised that there is high quality evidence in the over 6 age group. The new granule formulation has been shown to be safe in 2-5 year olds while achieving the same drug levels and the same affect on sweat chloride. Those treated showed improvement in their nutritional status. It has also just been licensed by the EMA in this age group, and due to the low number of patients who would be suitable for ivacaftor treatment, level 1 evidence is unlikely to become available to support the commissioning position.

## **1. Introduction**

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission Ivacaftor for children aged 2-5 years with 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 ivacaftor for children aged 2-5 years with cystic fibrosis 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 is the most common, life-limiting, recessively inherited disease in the UK, affecting c. 10,500 people. The underlying problem is a mutation in a gene that encodes for a chloride channel called the cystic fibrosis transmembrane conductance regulator (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 (Kalydeco, Vertex Pharmaceuticals) 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 the license was expanded again to include use of the granule formuation 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).

### **3. 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, marketed as Kalydeco by Vertex Pharmaceuticals, is a drug that treats the underlying cause of cystic fibrosis 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).

### **4. Aim and Objectives**

This policy proposition 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.

### **5. Epidemiology and Needs Assessment**

Cystic fibrosis is the most common, life-limiting, recessively inherited disease in the UK, affecting c. 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 CF transmembrane conductance regulator (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.

### 6. Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the 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:

- NHSE 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 such low patient numbers (66 in the UK) and it may not be possible to receive ethics board approval for a placebo controlled trial; 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 Cystic Fibrosis with one of the specified gating mutations. To date there are no Randomised Controlled Trials (RCT) in this paediatric population. However, there is high grade evidence (level -1/1) supporting the use of ivacaftor 150mg twice a day in children who have Cystic Fibrosis 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
- 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



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study (Davies et al, 2013) in which the mean paediatric age was 8.9 years of age also benefited from treatment, as improvements in lung function 12% of predicted FEV1 compared with standard care at 24 weeks were measured. There was significant weight gain of 2.7kg at 48 weeks and a very marked decrease in sweat chloride concentration (treatment effect -54.3mmol/L) which was most dramatic 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 Cystic Fibrosis 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 marked 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.

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 cystic fibrosis patients in England ranged from £438 million to £479 million for the lifetime cost and for standard care the lifetime cost was £72 million.

## 7. Proposed 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 70 mmol/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

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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.

## 8. Proposed 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.

## 9. Proposed Governance Arrangements

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

## 10. Proposed 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.

## 11. Proposed Audit Requirements

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.

## 12. Documents That Have Informed This Policy Proposition

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

## 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 (expected by June 2016).