NHS England

Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis (named mutations)

Reference: NHS England: A01/P/c

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Publications Gateway Reference:	**03706**
Document Purpose	Policy
Document Name	A01/P/c Ivacaftor for Cystic Fibrosis (G551D Mutation)
Author	Specialised Commissioning Team, NHS England
Publication Date	July 2015
Target Audience	Local Team Assistant Directors of Specialised Commissioning; Regional Team IFR Leads; Finance Leads; Local Team Pharmacists; Chairs of Clinical Reference Groups; Members of Clinical Reference Groups and registered stakeholders; Acute Trust Chief Executives; Acute Trust Medical Directors; Acute Trust Chief Pharmacists
Additional Circulation List	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
Description	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	A01/P/a
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	jeremyglyde@nhs.net for policy issues

Document Status

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1 Executive Summary

Policy Statement

NHS England will commission ivacaftor for the treatment of cystic fibrosis in patients aged six years and above who have at least one copy of one of nine named gene mutations in their gene for the protein called cystic fibrosis transmembrane conductance regulator (CFTR) in accordance with the criteria outlined in this document and only if the manufacturer provides it with the discount agreed.

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

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

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.

The treatments for CF that are currently available treat the symptoms of CF, such as chest infections. Ivacaftor is a new medicine that works differently and targets the production of the thick sticky mucus that causes many of the problems in CF. It is available to all patients, aged 6 years and older, with cystic fibrosis who have one of the following nine a certain type of faulty mutations in the CF gene:
G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D. There are only about 380 people in England who fit these criteria.

In three well conducted research studies ivacaftor improved lung function and resulted in patients gaining more weight. Two of the studies related specifically to the use of ivacaftor in patients with the G551D mutation, one involving adults and teenagers and one involving children. The study in adults also showed that fewer patients had a worsening of their breathing that needed to be treated by intravenous medicines or that needed hospital care. One study related specifically to the use of ivacaftor in patients aged 6 years and above with the G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D mutations, again showing improved lung function, weight and quality of life comparable to that seen in patients with the G551D mutation.

2 Introduction

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting about 10,000 people (7,700 in England). It predominantly affects the cells that 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 develop 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.

In cystic fibrosis, 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 problems with mucus secretion. Cystic fibrosis affects a number of organ systems.

Current standard 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.

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 £150m.

Ivacaftor (Kalydeco, Vertex Pharmaceuticals) is the first in a new class of medicines (CFTR potentiators) that target the cystic fibrosis CFTR and so treat the underlying cause of cystic fibrosis. Impaired functioning of this protein may be due to mutation of a number of different genes, the most common of which is ΔF508 mutation. This mutation occurs in around 75% of patients with CF in the UK. The G551D mutation occurs in around 4% whilst the other 8 non-G551D mutations for which ivacaftor is licenced together account for a further 0.56% of CF patients. Ivacaftor was designated as an orphan medicine in the EU in 2008. In July 2012, it received EU marketing authorisation for the "treatment 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)". In July 2014 the licence was extended to include patients aged 6 years and over with one of the following gene mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D. There are about 380 patients with these mutations in England.

3 Definitions

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting about 10,000 people (7,700 in England). It predominantly affects the cells that 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 develop 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.

4 Aims and Objectives

This policy aims to assess the clinical and cost-effectiveness of ivacaftor, within its marketing authorization, and determine the circumstances under which it will be funded by the NHS in England.

5 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 10,000 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.

CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene which was discovered in 1989.7 It sits on chromosome 7, is some 250kB in length, and encodes a protein of 1,480 amino acids. This protein is a chloride channel present at the surface of epithelial cells in multiple organs and is responsible for aiding in the regulation of salt and water absorption and secretion. Over 1,000 disease-causing alleles within this gene have been identified although only 23 have been demonstrated to cause sufficient loss of *CFTR* function to confer CF disease.

The most common mutation is the Δ*F508* mutation which is present on around 67% of CF chromosomes worldwide (75% in the UK).

The *G551D* (Glycine to Aspartate change in nucleotide 1784 in exon 11), affects approximately 4% of patients with CF in the UK. The other eight "gating" mutations listed in this document are rarer, affecting approximately 0.56% of UK CF patients. CFTR protein channels with these nine "gating" mutations have a greatly reduced fraction of time that the channel spends in the open state, or "open probability," and, therefore, have limited chloride transport ability.

Cystic fibrosis can be diagnosed through the sweat test, newborn screening or genetic testing. The sweat test tests for 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 (Δ*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.

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

A health technology assessment was commissioned through the NIHR HTA Programme (project number 12/32/01) to assess the clinical and cost effectiveness of ivacaftor for patients with the G551D mutation. A copy is available on request.

In summary:

1. In two pivotal randomised placebo-controlled trials (one in adults, one in children), and one open-label follow-up study, ivacaftor improved lung function, as measured using change in absolute % predicted Forced Expiratory Volume in 1 second (FEV1). Both adults and children had an increase in absolute % predicted FEV1 of around 10% compared with standard care, and this improvement was maintained during the follow-up study (96 weeks for adults, 72 weeks for children). See table 3 from the HTA report below.
2. In adults, compared with standard care, ivacaftor reduced the number of patients experiencing an exacerbation by 22%, and the total number of exacerbations by 70% (absolute risk reductions). The drug also reduced the number of exacerbations requiring intravenous therapy by 26% and those requiring hospitalisation by 15%. These data suggest that between 4 and 5 patients (the number needed to treat [NNT]) would need to be treated with ivacaftor plus standard care rather than standard care alone to prevent one patient having an exacerbation; for exacerbations requiring IV therapy and requiring hospitalisation, the NNTs are 4 and 7, respectively.
3. On average, adults and children treated with ivacaftor gained around 2.7kg more than those receiving standard care at 48 weeks follow-up.
4. Sweat chloride levels, used as a diagnostic indicator for cystic fibrosis, are normalised by ivacaftor.
5. The HTA calculated the incremental cost effectiveness ratio (ICER) for ivacaftor in a number of scenarios at its basic annual NHS price of £182,625. The range of ICERs was from £335,000 per QALY (optimistic scenario) to £1.274M per QALY (conservative scenario). This falls well outside the £20-30,000 per QALY threshold typically used to determine cost-effectiveness in the NHS.

6. Following the evaluation of the cost effectiveness of ivacaftor, Specialised Commissioners negotiated a discount which would improve the cost effectiveness of the treatment.

7. The agreed discount is a simple commercial in confidence price. This price will be reviewed in autumn 2015 or following a change in marketing authorization, whichever is the sooner.

At the discounted price, the range of ICERs for ivacaftor is £285,000 per QALY (optimistic scenario) to £1.077M per QALY. The ICER for the optimistic scenario falls within the range observed by NICE for other ultra-orphan medicines.

Table 3: Changes in lung function outcomes from baseline

Outcome	Study	Mean Change ivacaftor (SD)	Mean change placebo (SD)	MD in change (95% CI)	p-value*
24 weeks follow-up					
% Predicted FEV_1: absolute change	Adults	10.4	-0.2	10.6 (8.6, 12.6)	<0.0001
	Children	12.6	0.0	12.5 (6.6, 18.3)	<0.0001
% Predicted FEV_1: relative change (%)	Adults	17.6	0.7	16.9 (13.6, 20.2)	<0.0001
	Children	21.7	4.3	17.4 (NR)	<0.0001
FEV_1(L)	Adults	0.4	0.0	0.4 (0.3, 0.4)	<0.0001
48 weeks follow-up					
% Predicted FEV_1: absolute change	Adults	10.1	-0.4	10.5 (8.5, 12.5)	<0.0001
	Children	NR	NR	10.0 (4.5, 15.5)	0.0006
% Predicted FEV_1: relative change (%)	Adults	17.5	0.8	16.8 (13.5, 20.1)	<0.0001
	Children	NR	NR	15.1(NR)	NR
FEV_1(L)	Adults	0.4	0.0	0.4 (0.3, 0.4)	<0.0001

* p-values based on mixed-effects model for repeated measures; analysis in children unclear

Following the extension of the licence for ivacaftor to include the gene mutations G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D the Cystic Fibrosis Clinical Reference Group, assisted by Public Health England, conducted an evidence review of the effectiveness of ivacaftor in the treatment of these mutations. A copy of the evidence review is available on request. In summary the evidence review assessed:

In patients with cystic fibrosis aged 6 years and over, who have at least one of these specific additional 8 non-G551D gating mutations, and a minimum FEV1 of 40% of

that predicted at screening, does treatment with ivacaftor, when compared to placebo and/or standard therapy improve the following outcomes:

1) Lung function as assessed by absolute or relative change in FEV1 (absolute or percent predicted), or other appropriate measure such as FEF25-75 or lung clearance index.
   Patients receiving ivacaftor demonstrated a 10.7% mean percentage point difference in FEV1 compared to placebo at 8 weeks (95% CI 7.3; 14.1). By the end of the additional 16 week open label study the mean absolute change from baseline in %-predicted FEV1 was 13.5 percentage points (wide range of values). See Table 3 for appraisal of evidence. (De Boeck 2014)
   SIGN Level of Evidence 1++, SIGN grade of Evidence A.

2) Rate of pulmonary exacerbations (appropriate protocol defined, for example Fuch's criteria; additional pulmonary symptoms or signs requiring use of oral and/or intravenous antibiotics).
   This was not formally assessed as an outcome measure. However, data were collected through the adverse event reporting process demonstrating fewer pulmonary exacerbations in the subjects with non-G551D gating mutations receiving ivacaftor. Pulmonary exacerbations were seen in 9/38 (23.7%) of the patients treated with Ivacaftor compared to 11/37 (29.7%) of the patients receiving placebo. See Table 4 for appraisal of evidence. (De Boeck 2014)
   SIGN Level of Evidence 1++, SIGN Grade of Evidence B.

3) Nutrition as measured by improvement in weight or BMI centile position (or absolute weight if appropriate for population)
   Patients receiving ivacaftor showed an improved BMI of 0.7 kg/m2 compared to placebo at week 8 ($p<0.0001$), with absolute change from baseline BMI of 1.3 kg/m2 by week 24. BMI for age z score (model adjusted) also improved, with a treatment effect at week 8 of 0.28 ($P=0.001$). See Table 3 for appraisal of evidence. (De Boeck 2014)
   SIGN Level of Evidence 1++, SIGN grade of Evidence A.

4) Quality of life as measured by validated score
   CFQ-R Respiratory Domain was significantly greater in patients receiving ivacaftor with a treatment difference to placebo of 9.6 points (p = 0.0004), and mean being 11.4 points better than baseline at week 24. Improvements in Quality of Life score were seen as early as 2 weeks into ivacaftor treatment. An improvement in CFQ-R score of >4 points is regarded as clinically significant, by week 8 this was seen in 73.7% of those on ivacaftor and only 29.7% of those on placebo. See Table 3 for appraisal of evidence. (De Boeck 2014)
   SIGN Level of Evidence 1++, SIGN grade of Evidence A.

5) Where measured an appropriate measure of CFTR function for example sweat chloride, nasal potential difference, intestinal current measurement etc.
   Sweat chloride treatment effect of ivacaftor was -49.2 mmol/L, p<0.0001 at week 8 compared to placebo, absolute change from baseline at week 24 was -59.2 mmol/L. This significant decrease in sweat chloride was seen from week 2 in those subjects receiving ivacaftor. See Table 3 for appraisal of evidence. (De Boeck 2014)
   SIGN Level of Evidence 1++, SIGN grade of Evidence A.

6) Comparable efficacy to that seen with Ivacaftor for patients with Cystic Fibrosis aged 6 years and over who have one or more copies of the G551D mutation (already funded through NHS England)
   Ivacaftor was licensed and funded for patients with at least one G551D mutation based on the impressive efficacy seen in two pivotal papers (Ramsey et al. 2011 studying G551D patients aged 12 years and older; and Davies et al. 2013 studying G551D patients aged 6-11 years).
   The increases in percent predicted FEV1 in these papers were 10.6 and 12.5 percentage points respectively by week 24. Thus the 13.5 percentage points increase from baseline seen with ivacaftor after the 16 week open label phase of the De Boeck study focusing on the other non-G551D gating mutations is a comparable improvement.

With respect to change in BMI, this was not reported by Ramsey, who instead evaluated weight gain, demonstrating a 2.7 kg weight gain by 48 weeks in patients receiving ivacaftor compared to those receiving placebo (P<0.001), steadily improving to this amount through the course of the 48 weeks. Davies reported a BMI for age z-score treatment effect at 24 weeks of 0.34 (P<0.001), increasing again through the course of the study to 0.45 by week 48. De Boeck reported a BMI for age z-score treatment effect of 0.28 by week 8 (P=0.001), which given the earlier time-point of analysis appears a comparable level of efficacy.

Sweat chloride improved by a mean of −48.1 mmol per litre (P<0.001) and -53.5 mmol/L (P < 0.001) versus placebo, in the Ramsey and Davies G551D studies respectively. In non-G551D gating mutation subjects (De Boeck 2014) the change is comparable (-49.2 mmol/L, p<0.0001 at week 8 compared to placebo, absolute change from baseline at week 24 was -59.2 mmol/L).

Similarly for the CFQ-R Respiratory Domain patient reported quality of life score, these improved by 8.6 points (P<0.01) in Ramsey 2011, by 6.1 (not statistically significant; P=0.109) in Davies 2013, and by 9.6 points (p = 0.0004) compared to placebo in the non-G551D gating mutation subjects (De Boeck 2014).

Ramsey reported G551D subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients receiving placebo, through week 48 (P<0.001). Davies reported a low level of pulmonary exacerbations in children with G551D aged 6-11years which did not differ between the treatment groups. This was not assessed as an outcome measure in the De Boeck study, but through the adverse event monitoring system it can be seen that in this relatively small sample size that there were fewer pulmonary exacerbations in the subjects with non-G551D gating mutations receiving ivacaftor (Pulmonary exacerbations were seen in 23.7% of Ivacaftor group and 29.7% of placebo group).

SIGN Level of Evidence 1++, SIGN Grade of Evidence B.

7) Is safety profile acceptable with benefit outweighing risk of therapy in patients with one or more of these specific 8 non-G551D gating mutations?
In part 1 of the De Boeck study adverse events occurred in 73.7% of patients on ivacaftor and 83.8% of those taking placebo. Pulmonary exacerbations were seen in 23.7% of the ivacaftor group and 29.7% of the placebo group. Cough occurred in 15.8% of those on ivacaftor and 18.9% of those in placebo group. Serious adverse events (pulmonary exacerbation requiring hospitalisation; surgical events etc) occurred in 10.5% of the ivacaftor group and in 18.9% of the placebo group. In the 16 week follow-on study, for those completing 24 continuous weeks of ivacaftor, cough was seen in 16.7% and pulmonary exacerbation was also seen in 16.7%. Thus safety profile seems good. (De Boeck 2014)
SIGN Level of Evidence 1++, SIGN grade of Evidence A.

Additionally, in cystic fibrosis subjects with the G551D mutation there is now considerable safety data available. Ramsey reported a similar incidence of adverse effects with ivacaftor and placebo, with a lower proportion of serious adverse events with ivacaftor than with placebo (24% vs. 42%)(Ramsey 2011). Similarly Davies reported adverse events to be similar between ivacaftor and placebo groups through to week 48 in children aged 6-11 years with the G551D mutation. Furthermore robust monitoring of all NHS patients in England receiving ivacaftor occurs through the UK CF Registry. This demonstrates that of 358 patients who were on ivacaftor in July 2014, 293 of whom had started since 01/01/2013, only 2 patients have stopped ivacaftor due to side effects (one insomnia; one severe insomnia)(Use of Ivacaftor in England: Interim Review. UK CF Registry 2014).

Overall the evidence review concluded:

This Evidence Review finds SIGN Level 1++ and Grade A Evidence to support clinical effectiveness and safety of ivacaftor 150mg orally twice daily for people with cystic fibrosis aged 6 years and over who have one of 8 specific non-G551D gating

mutations (G178R; S549N; S549R; G551S; G1244E; S1251N; S1255P; G1349D), and a minimum FEV1 of 40% of that predicted at screening. The clinical severity of these Cystic Fibrosis causing mutations is severe and similar to G551D (mean sweat chloride at baseline 97.5mmol/L; proportion of subjects with pancreatic insufficiency 79.5%, [De Boeck 2014)) compared to G551D (data from CFTR 2: mean sweat chloride 102mmol/L; proportion of subjects with pancreatic insufficiency 93%). A cost effectiveness evaluation has previously been performed for ivacaftor in G551D subjects (Whiting et al. 2012). The Evidence Review concludes that the clinical effectiveness of ivacaftor, when used for this newly licensed indication, is comparable to the clinical effectiveness of ivacaftor when used in patients with the G551D gene mutation.

7 Rationale behind the Policy Statement

There is good evidence that ivacaftor is clinically effective for patients with the 9 gene mutations for which it is licensed. The availability of long-term safety data have improved.

Ivacaftor is very expensive but commissioners noted the views of specialist clinicians and the potential benefits to eligible patients. Commissioners also noted that the NHS currently funds a number of other 'ultra-orphan medicines' that have high opportunity cost and with incremental cost effectiveness ratios likely to fall in the same range as ivacaftor.

Ivacaftor will only be funded if it is made available in accordance with an agreed discount and in accordance with a revised agreement reached with the manufacturer following the extension of the licence.

Health outcomes in patients taking ivacaftor will be monitored using data from the CF registry. The first monitoring report on the use of ivacaftor in patients with G551D was compiled and issued to NHS England in July 2014. Subsequent reports will be included in the CF Registry Annual Reports.

8 Criteria for Commissioning

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

Ivacaftor will be routinely commissioned for all patients in England who are aged 6 years and older with cystic fibrosis and at least one copy of one of the following gene mutations: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D. It will be funded only if the manufacturer provides it with the discount agreed and in accordance with the revised agreement reached in February 2015. Ivacaftor will only be prescribed by a specialist centre. It is not suitable for shared-care prescribing by the patient's GP.

All patients must have had a sweat chloride test within the 6 months prior to starting treatment and be informed of the stopping criteria at the time of starting treatment with ivacaftor.

In the rare event that a baseline sweat chloride reading cannot be determined, the patient may be commenced on treatment and response based on changes in lung function only (criteria (d) below).

Stopping criteria

The sweat chloride test will be repeated at the next routine review appointment after starting ivacaftor to determine whether sweat chloride levels are reducing and to check compliance with drug regimen. The sweat chloride level will then be re-

checked 6 months after starting treatment to determine whether the full reduction (as detailed below) has been achieved. Thereafter sweat chloride levels will be checked annually.

The patients will be considered to have responded to treatment if either

a) the patient's sweat chloride test falls below 60mmol/litre **OR**

b) the patient's sweat chloride test falls by at least 30%. In cases where the sweat chloride is reduced but does not fall below 60mmol/litre or by at least 30% then the patients' response will be based on changes in lung function of an absolute change in FEV1 of at least 5%. Clinicians agree that an absolute change in FEV1 of at least 5% is clinically significant.

In cases where the baseline sweat chloride test is already below 60mmol/litre, the patient will be considered to have responded to treatment if either

c) the patient's sweat chloride test falls by at least 30% **OR**

d) the patient demonstrates a sustained absolute improvement in FEV1 of at least 5%. In this instance FEV1 will be compared with the baseline pre-treatment level one month and three months after starting treatment.

If the expected reduction in sweat chloride or improvement in lung function does not occur, the patient's CF clinician will first explore any problems in following the recommended dosing schedule for ivacaftor. The patient's sweat chloride will then be retested around one week later and treatment discontinued if the patient does not meet the above criteria.

9 Patient Pathway

Ivacaftor will be considered as an option for all patients aged 6 years and older with cystic fibrosis and one of the nine named gene mutations in this policy. It will be added to existing standard treatment. Treatment will continue unless the patient meets stopping criteria described above.

10 Governance Arrangements

See national service specification for cystic fibrosis services.

11 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, subject to the discount agreed with the manufacturer.

12 Audit Requirements

As for CF registry.

13 Documents which have informed this Policy

Whiting P, Al M, Burgers L, Westwood ME, Ryder S, Hoogendoorn M, Armstrong N, Allen A, Severens J, Kleijnen J. Ivacaftor for the Treatment of Patients with Cystic Fibrosis and the G551D Mutation: A Health technology Assessment Report. Kleijnen Systematic Reviews Ltd., 2012.

De Boeck K, Munck A, Walker S, et al. Efficacy and Safety of Ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros 2014; 13: 674-680

Ramsey BW, Davies J, McElvaney G, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. New England Journal of Medicine 2011; 365: 1663-1672

Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and Safety of Ivacaftor in patients aged 6 - 11 years with cystic fibrosis with a G551D mutation. Am J Resp Crit Care Med 2013; 187: 1219-1225

Use of Ivacaftor in England: Interim Review. UK CF Registry 06/08/2014

14 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).

15 Date of Review

The discount was due to be reviewed in the autumn of 2015. As the licence for ivacaftor has been extended to include the 8 named non-G551D gating mutations, and additional commercial in confidence arrangement has been agreed with the manufacturer which covers the period to the end of March 2018. This policy will therefore be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

1. Whiting P, Al M, Burgers L, Westwood ME, Ryder S, Hoogendoorn M, Armstrong N, Allen A, Severens J, Kleijnen J. Ivacaftor for the Treatment of Patients with Cystic Fibrosis and the G551D Mutation: A Health technology Assessment Report. Kleijnen Systematic Reviews Ltd., 2012.

2. De Boeck K, Munck A, Walker S, et al. Efficacy and Safety of Ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros 2014; 13: 674-680

3. Ramsey BW, Davies J, McElvaney G, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. New England Journal of Medicine 2011; 365: 1663-1672

4. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and Safety of Ivacaftor in patients aged 6 - 11 years with cystic fibrosis with a G551D mutation. Am J Resp Crit Care Med 2013; 187: 1219-1225

5. Use of Ivacaftor in England: Interim Review. UK CF Registry 06/08/2014