NHS Commissioning Board

Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis

First published: March 2013

Prepared by the North of England Specialised Commissioning Group
(Yorkshire and the Humber office) for the four Specialised Commissioning Groups in England

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First published March 2013
Published by the NHS Commissioning Board, in electronic format only.
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Policy Statement

Ivacaftor will be routinely commissioned 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) in accordance with the criteria outlined in this document and only if the manufacturer provides it with the discount agreed in the Patient Access Scheme.

In creating this policy the Specialised Commissioning Groups of England have 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

The NHS CB 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. The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB 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 they are 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 7,300 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 into 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 a certain type of faulty gene, called G551D mutation. There are only about 320 people in England who fit these criteria.

In two well conducted research studies, one involving adults and one involving children, ivacaftor improved lung function and resulted in patients gaining more weight. 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.

We don’t yet know if ivacaftor stops people dying early with CF as studies haven’t followed people for long enough. But we do know that the amount of salt produced in sweat, the main indicator of cystic fibrosis, returns to normal when a patient starts to take ivacaftor.
1. Introduction

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting about 9,000 people (7,300 in England). It 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 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.

In cystic fibrosis, the underlying problem is 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 £100m.

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 ∆F508 mutation. This mutation occurs in around 75% of patients with CF in the UK; the G551D mutation occurs in around 4%.

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)". There are about 320 patients with the G551D mutation in England, around 270 of whom are aged 6 years or over.
2. Aim and objectives

To assess the clinical and cost-effectiveness of ivacaftor, within its marketing authorisation, and determine the circumstances under which it will be funded by the NHS in England.

3. Criteria for commissioning

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 the G551D gene mutation. It will be funded only if the manufacturer provides it with the discount agreed in the Patient Access Scheme.

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 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 pretreatment level one month and three months after starting treatment.
If the expected reduction in sweat chloride 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.

4. Patient pathway

Ivacaftor will be considered as an option for all patients aged 6 years and older with cystic fibrosis and G551D mutation. It will be added to existing standard treatment. Treatment will continue unless the patient meets stopping criteria described above.

5. Governance arrangements

See national service specification for cystic fibrosis services.

6. 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.

CF is caused by mutations in the CF transmembrane conductance regulator (CFTR)
gene which was discovered in 1989. 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 \textit{CFTR} function to confer CF disease. The most common mutation is the $\Delta F508$ mutation which is present on around 67\% of CF chromosomes worldwide.

The \textit{G551D} (Glycine to Aspartate change in nucleotide 1784 in exon 11), affects approximately 5.7\% of patients with CF in the UK. \textit{CFTR} protein channels with the \textit{G551D} mutation 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 \textit{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 ($\Delta F508$, \textit{G551D}, \textit{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.
7. Evidence base

A health technology assessment was commissioned through the NIHR HTA Programme (project number 12/32/01). 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. NB data highlighted in yellow are provided in confidence and should not be shared outside NHS decision-making groups.

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 worked with Vertex to develop a Patient Access Scheme which would improve the cost effectiveness of the treatment.

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

8. 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.
8. Rationale behind the policy statement

There is good evidence that ivacaftor is clinically effective for patients with the G551D gene mutation although long-term safety and effectiveness data beyond 96 weeks are lacking.

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 Patient Access Scheme and there will be no financial impact on commissioning organisations in 2012/13. The NHSCB has indicated that future funding of ivacaftor will be included as part of its legacy arrangements.

Health outcomes in patients taking ivacaftor will be monitored using data from the CF registry.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Mean Change ivacaftor (SD)</th>
<th>Mean change placebo (SD)</th>
<th>MD in change (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 weeks follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Predicted FEV1: absolute change</td>
<td>Adults</td>
<td>10.4</td>
<td>-0.2</td>
<td>10.6 (8.6, 12.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>12.6</td>
<td>0.0</td>
<td>12.5 (6.6, 18.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Predicted FEV1: relative change (%)</td>
<td>Adults</td>
<td>17.6</td>
<td>0.7</td>
<td>16.9 (13.6, 20.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>21.7</td>
<td>4.3</td>
<td>17.4 (NR)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1(L)</td>
<td>Adults</td>
<td>0.4</td>
<td>0.0</td>
<td>0.4 (0.3, 0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>48 weeks follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Predicted FEV1: absolute change</td>
<td>Adults</td>
<td>10.1</td>
<td>-0.4</td>
<td>10.5 (8.5, 12.5)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>Children</td>
<td>NR</td>
<td>NR</td>
<td>10.0 (4.5, 15.5)</td>
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<tr>
<td>% Predicted FEV1: relative change (%)</td>
<td>Adults</td>
<td>17.5</td>
<td>0.8</td>
<td>16.8 (13.5, 20.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>NR</td>
<td>NR</td>
<td>15.1 (NR)</td>
<td>NR</td>
</tr>
<tr>
<td>FEV1(L)</td>
<td>Adults</td>
<td>0.4</td>
<td>0.0</td>
<td>0.4 (0.3, 0.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* p-values based on mixed-effects model for repeated measures; analysis in children unclear.
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, subject to the terms of the Patient Access Scheme.

10. Audit requirements

As for CF registry.

11. Documents which have informed this policy


12. Links to other policies

N/A

13. Date of review

Patient Access Scheme to be reviewed by autumn 2015

References