Clinical Commissioning Urgent Policy Statement
Cystic Fibrosis Modulator Therapies Access Agreement for licensed mutations [200810P]

Commissioning position

Summary

NHS England provides through an access agreement the cystic fibrosis modulator therapies: Ivacaftor; lumacaftor/ivacaftor; and tezacaftor/ivacaftor for patients in England as defined by their marketing authorisations. This updated policy includes access to the triple therapy elexacaftor/tezacaftor/ivacaftor according to the European marketing authorisation and other revisions to the market authorisations for these products since the policy was first published.

Information about cystic fibrosis modulator therapies

The intervention

There are four modulator therapies with market authorisations that act on the cystic fibrosis transmembrane conductance regulator (CFTR) pathways and ameliorate the impact of specific defective genes that result in the absence or dysfunction of the CFTR protein, a cell-surface localised chloride channel that regulates salt and water absorption and secretion across epithelia in multiple organs.

The condition

Cystic fibrosis (CF) is an inherited, multi-system, genetic condition that causes a build-up of sticky mucus in the lungs, digestive system and other organs. People with cystic fibrosis can experience a range of symptoms throughout the body. In the lungs, the build-up of mucus can cause chronic infections, whilst in the digestive system excess mucus can cause a difficulty in digesting food. Cystic fibrosis can have a significant impact on life expectancy and quality of life (NICE guideline on cystic fibrosis).

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that result in the absence or dysfunction of the CFTR protein, a cell-surface localised chloride channel that regulates salt and water absorption and secretion across epithelia in multiple organs. This loss of chloride transport leads to the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction and elevated sweat chloride concentration (Van Goor et al. 2014). The leading cause of mortality in people with cystic fibrosis is the progressive loss of lung function.

Many different mutations are responsible for cystic fibrosis. Disease severity generally correlates with the severity of the loss of chloride transport. Complete, or near complete loss of CFTR-mediated chloride transport is referred to as ‘minimal function’ of CFTR protein and results in severe cystic fibrosis.

Current treatments

There are four modulator therapies that act on the cystic fibrosis transmembrane conductance regulator (CFTR) pathways:

1. Ivacaftor is a CFTR potentiator, meaning it increases the activity of the defective CFTR protein. This means that ivacaftor increases the chances that the defective channel will open on the cell surface and let chloride and sodium ions pass through. It has market authorisation for patients 6 months and above who have an R117H CFTR mutation or one of the named gating (class III) mutations in the CFTR gene. The likelihood of the R117H mutation causing clinical CF disease is also dependant on the genetic variation in another gene (the polythymidine repeat sequence on Intron 8). Ivacaftor therapy is commissioned for CF patients who have the R117H CF gene mutation and have clinical, biochemical or electro physiological evidence of CF disease and excludes inconclusive diagnosis (CFSPID).

2. Lumacaftor/ivacaftor is a systemic protein modulator. Lumacaftor is a corrector of the cystic fibrosis transmembrane conductance regulator (CFTR) working in combination with ivacaftor as a potentiator of the CFTR. Lumacaftor/ivacaftor has a marketing authorisation in the UK for treating cystic fibrosis in people 2 years and older who are homozygous for the F508del mutation in the CFTR gene.
3. Ivacaftor/tezacaftor (used in combination with ivacaftor): tezacaftor is designed to move the defective CFTR protein to the correct position in the cell. It is for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation mutations in the CFTR gene or heterozygous for the F508del mutation combined with one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.
4. Elexacaftor/tezacaftor/ivacaftor (used in combination with ivacaftor). The triple therapy is designed to act a potentiator and a corrector. It is for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation combined with a minimal function gene mutation (MF) corresponding to either no production of a CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor in vitro.

For all these CFTR products where the EMA license is amended in the future, eligible patients will automatically have access under those terms.

Marketing Authorisations

Ivacaftor (Kalydeco®): 150mg tablets (link); granules (link)

Ivacaftor/lumacaftor (Orkambi®): tablets (link): granules (link)

Ivacaftor/tezacaftor (Symkevi®): Used in combination with ivacaftor (link)

Elexacaftor/tezacaftor/ivacaftor (Kaftrio®): tablets used in combination with ivacaftor (insert

EMA link when confirmed)

Clinical Trial Evidence

NHS England has previously considered the evidence base for ivacaftor for 9 “gating” mutations and for the R117H mutation. NICE has published a Technology Appraisal 398 on the clinical effectiveness of lumacaftor/ivacaftor (link).

Adverse events

The marketing authorisations for each product cover side effects, contra-indications, drug interactions, and the need to consider variation in dosing when ivacaftor is given in combination with other products as well as limiting use to specific age ranges.

Implementation

Criteria

Ivacaftor, lumacaftor/ivacaftor and tezacaftor/Ivacaftor and elexacaftor/tezacaftor/ivacaftor must only be prescribed by physicians with experience in the treatment of cystic fibrosis working within NHS England commissioned CF services in line with the respective market authorisations. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed before starting treatment to confirm the presence of an indicated mutation in the *CFTR* gene. CF Clinical teams will need to review existing patients prior to changing or initiating new medications.

Eligibility and dosing within the EMA license

The CF mutations eligible for treatment are listed in the Tables below.
For elexacaftor/tezacaftor/ivacaftor to support clinical teams a reference list of mutations will be made available to assist clinicians in determining eligibility within the access agreement.

<table>
<tr><td colspan="4">Table 1 Ivacaftor as a monotherapy: for patients aged 6 months and over</td></tr>
<tr><td colspan="4">In adults, adolescents, and children aged 6 years and older and weighing 25 kg or more
The recommended dose is one 150 mg tablet taken orally every 12 hours (300 mg total daily dose) with fat-containing food.</td></tr>
<tr><td colspan="4">Infants aged at least 6 months, toddlers, children, adolescents and adults should be dosed according to the patients weight but weighing 5 kg to less than 25 kg
≥5 kg to < 7 kg: 25 mg granules taken orally every 12 hours with fat-containing food
≥ 7 kg to < 14 kg: 50 mg granules taken orally every 12 hours with fat-containing food
≥ 14 kg to < 25 kg: 75 mg granules taken orally every 12 hours with fat-containing food
≥ 25 kg: See ivacaftor tablets SmPC for further details.</td></tr>
<tr><td rowspan="4">Heterozygous for the class III “gating” mutations or R117H</td><td>G551D</td><td>G178R</td><td>S549N,</td></tr>
<tr><td>S549R</td><td>G551S</td><td>G1244E</td></tr>
<tr><td>S1251N</td><td>S1255P</td><td>G1349D</td></tr>
<tr><td colspan="3">R117H but excluding CFSPID</td></tr>
</table>

Table 2 Lumacaftor / ivacaftor as a combination therapy: for patients aged 2 years and over	
12 years and older Two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours	
6 to 11 years Two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours	
2 to 5 years and weighing less than 14 kg One lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours 2 to 5 years and weighing 14 kg or greater One lumacaftor 150 mg/ivacaftor 188 mg sachet every 12 hours	
Named Mutations	Homozygous for the F508del mutation

Table 3 Tezacaftor / ivacaftor as a combination therapy			
Adults and adolescents aged 12 years and older In a combination regimen with ivacaftor 150 mg tablets The recommended dose is one tezacaftor 100 mg/ivacaftor 150 mg tablet taken in the morning and one ivacaftor 150 mg tablet taken in the evening, approximately 12 hours apart with fat-containing food (see Method of administration).			
Named Mutations	Homozygous for the F508del mutation		
	Heterozygous for the F508del mutation combined with one of the following mutations:		
	P67L	R117C	L206W
	R352Q	A455E	D579G
	S945L	S977F	R1070W
	D1152H	2789+5G→A	3272-26A→G,
	3849+10kbC→T		

Table 4 Elexacaftor / tezacaftor / ivacaftor as a combination therapy	
Adults and adolescents aged 12 years and older The recommended dose is two tablets (each containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg) taken in the morning and one ivacaftor tablet (containing ivacaftor 150 mg) taken in the evening, approximately 12 hours apart. It is for oral use and the tablet should be swallowed whole. It should be taken with fat-containing food.	
Named Mutations	Homozygous for the F508del mutation
	Heterozygous for the F508del mutation combined with a minimal function mutation

Clinicians should refer to the current Summary of Product Characteristics before prescribing and for dose modifications if patients are on other therapies or have co-morbidities.

Effective from

This urgent policy statement will be effective from the date of publication.

Recommendations for data collection

Data collection as part of the access agreement will be used by NICE to inform further evaluation of lumacaftor/ivacaftor and to support a clinical and cost effectiveness evaluation of tezacaftor/ivacaftor. NICE will extend data collection to support a clinical and cost effectiveness evaluation of elexacaftor/tezacaftor/ivacaftor.

The Cystic Fibrosis Trust manages the CF Registry and data for these therapies will be collected in the same way. NICE will confirm the final data collection agreement to support the evaluation process across all treatments.

Mechanism for funding

NHS England will fund these treatments for eligible patients as per the therapeutic indications within the current and future marketing authorisations for each of the four products.

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted on ivacaftor/tezacaftor at this stage; and public consultation has not been undertaken on ivacaftor for R117H mutation or ivacaftor/tezacaftor. This policy statement will be reviewed after NICE has completed the evaluations for ivacaftor, lumacaftor/ ivacaftor and ivacaftor/ tezacaftor and elexacaftor/tezacaftor /ivacaftor.

Links to other Policies

This document replaces the published policy: 190137P Cystic Fibrosis Modulator Therapies.

Patients not eligible for treatment under this policy may be eligible under the Urgent Policy Statement Ivacaftor and tezacaftor/ivacaftor for Cystic Fibrosis: unlicensed use in patients with named rarer mutations: 200809P.

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.