Clinical Commissioning Urgent Policy Statement
Cystic Fibrosis Modulator Therapies

NHS England URN: 190137P

Commissioning Position

NHS England will routinely commission the cystic fibrosis modulator therapies: Ivacaftor; Lumacaftor/Ivacaftor; and Tezacaftor/Ivacaftor for patients in England as defined by their marketing authorisations.

Information about Cystic Fibrosis Modulator Therapies

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

Committee Discussion

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 CF can experience a range of symptoms throughout the body. In the lungs, the build-up of mucus can cause chronic infections, and in the digestive system excess mucus can cause a difficulty in digesting food. CF can have a significant impact on life expectancy and quality of life (NICE guideline on cystic fibrosis).

CF 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 passages (bronchi) of the lungs, loss of pancreatic function, impaired intestinal absorption, reproductive difficulties and elevated sweat chloride concentration (Van Goor et al. 2014). The leading cause of mortality in people with CF is the progressive loss of lung function.

Many different gene mutations are responsible for CF and result in different disease severity and the CFTR modulator therapies act on different parts of the pathway. Disease severity generally reflects 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 and results in severe CF. Moderate loss of CFTR-mediated chloride transport is referred to as ‘residual chloride function’ and results in less severe disease.

Current treatments

There are three modulator therapies that act on the 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 aged one year and above who have at least one copy of the

2. Lumacaftor/Ivacaftor is a systemic protein modulator. Lumacaftor is a corrector of the CFTR working in combination with ivacaftor as a potentiator of the CFTR. Lumacaftor/Ivacaftor has a marketing authorisation in the UK for treating CF in people 2 years and older who have 2 copies of 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 CF aged 12 years and older who have 2 copies of the F508del mutation or one copy of 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.

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)

Evidence of Effectiveness
NHS England has previously considered the evidence base for Ivacaftor for 9 “gating” mutations and for the R117H mutation. The National Institute for Health and Care Excellence (NICE) has published a Technology Appraisal 398 on the clinical effectiveness of lumacaftor/ivacaftor (link).

Safety
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 should only be prescribed by physicians with experience in the treatment of CF working within NHS England commissioned CF services and 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.

Effective from
11 November 2019

Recommendations for data collection
Data collection will be used by NICE to inform further evaluation of Lumacaftor/Ivacaftor and to support a clinical and cost effectiveness evaluation of Tezacaftor/Ivacaftor. The Cystic Fibrosis Trust manages the CF Registry and it is envisaged data for these therapies will be collected in the same way. NICE will confirm the final data collection agreement to support the evaluation process.

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 three 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 Lumacaftor/Ivacaftor and Ivacaftor/Tezacaftor.

Links to other Policies

This document replaces the existing published policies for ivacaftor as a CFTR modulator therapy for adults and children over 2 years old with CF.

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.