NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Evaluation

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of ivacaftor–tezacaftor–elexacaftor (Kaftrio), tezacaftor–ivacaftor (Symkevi) and lumacaftor–ivacaftor (Orkambi) within their marketing authorisations for treating cystic fibrosis.

Background

Cystic fibrosis is an inherited disease caused by genetic mutations. The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene normally creates a protein that regulates levels of sodium and chloride in cells. If the *CFTR* gene is faulty, cells are unable to make functioning versions of this protein, leading to a build-up of thick, sticky mucus in the body's tubes and passageways. These blockages damage the lungs, digestive system and other organs, resulting in persistent cough, recurring chest and lung infections and poor weight gain. Cystic fibrosis is a progressive condition that limits life expectancy.

Cystic fibrosis affects about 10,000 people in the UK.[1] About 1 in 25 people are carriers of a faulty gene (or 'mutation') that can cause cystic fibrosis.[2] There are over 2,000 known mutations that can cause cystic fibrosis.[3] For someone to be born with cystic fibrosis, they must inherit a faulty gene from both parents. These mutations can either be homozygous, the same, or heterozygous, different mutations. The most common mutation is the *F508del* mutation and around 9714 (89%) people with cystic fibrosis carry at least 1 copy of the *F508del* mutation.[1]

Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease. Treatments can be broadly classified as: nutritional repletion (for example, pancreatic enzymes and nutritional supplements); relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators); treatment of acute infections; suppression of chronic infection; suppression of inflammation (for example, steroids, high dose ibuprofen) and organ transplantation, including lung, liver or pancreas. NICE technology appraisal 266 recommends mannitol dry powder for inhalation as an option for some people with cystic fibrosis in adults. NICE technology appraisal 276 recommends colistimethate sodium and tobramycin dry powders for inhalation for treating chronic lung infections in some people with cystic fibrosis.

Ivacaftor was first made available to selected NHS patients in 2013. In October 2019, NHS England & Improvement announced they and Vertex have concluded an access agreement to enable eligible patients in England interim access to treatment with, tezacaftor–ivacaftor, lumacaftor–ivacaftor via the NHS while further data are collected. In August 2020, ivacaftor–tezacaftor–elexacaftor was also made available via the NHS through this agreement. As access was agreed for current and future possible licence extensions, in January 2022, children with cystic fibrosis aged 6 to

11 were able to access ivacaftor–tezacaftor–elexacaftor following a licence extension.

An NHS England commissioning statement also outlines the circumstances when NHS England will reimburse the off-label use of ivacaftor, tezacaftor–ivacaftor and ivacaftor–tezacaftor–elexacaftor. [4]

The technologies

Ivacaftor, tezacaftor and elexacaftor combination therapy (Kaftrio, Vertex Pharmaceuticals) is a systemic protein modulator. The combination is administered orally. It has a marketing authorisation in the UK 'in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene'. Elexacaftor, tezacaftor and ivacaftor combination therapy has also been studied in a Phase III clinical trial in children who are at least 2 years old and less than 5 years old with cystic fibrosis who have at least one *F508del* mutation.

Tezacaftor and ivacaftor combination therapy (Symkevi, Vertex Pharmaceuticals) is a systemic protein modulator. The combination is administered orally. It has a marketing authorisation in the UK 'in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*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'*.

Lumacaftor and ivacaftor combination therapy (Orkambi, Vertex Pharmaceuticals) is a systemic protein modulator. The combination is administered orally as tablets or granules. Lumacaftor–ivacaftor tablets have a marketing authorisation in the UK for treating 'cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene'. Lumacaftor–ivacaftor granules have a marketing authorisation in the UK for treating 'cystic fibrosis (CF) in patients aged 2 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene'. Lumacaftor and ivacaftor combination therapy has also been studied in a Phase III clinical trial in children who are at least 1 years old and less than 2 years old with cystic fibrosis who are homozygous for the *F508del* mutation.

Interventions	• Ivacaftor, tezacaftor and elexacaftor combination therapy (Kaftrio) • Tezacaftor and ivacaftor combination therapy (Symkevi) • Lumacaftor and ivacaftor combination therapy (Orkambi)
Population	People with cystic fibrosis with at least one *F508del* mutation

Subgroups	People who are • homozygous for the *F508del* mutation, or • heterozygous for the *F508del* mutation and a residual function mutation or gating mutation
Comparators	Established clinical management including: • best supportive care • mannitol dry powder for inhalation • inhaled mucolytics • nebulised hypertonic saline • anti-inflammatory agents • bronchodilators • vitamin supplements • pancreatic enzymes For people with a gating mutation: • ivacaftor monotherapy[a] The interventions will be compared to each other
Outcomes	The outcome measures to be considered include: • mortality • change in the percentage of predicted forced expiratory volume • forced vital capacity • lung function, including transplantation • body mass index • respiratory symptoms • pulmonary exacerbations, including frequency and severity of acute infections • sweat chloride • lung clearance index 2.5 • pulmonary bacterial colonisation • need for hospitalisation and other treatments including antibiotics • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.
Related NICE recommendations	**Related Technology Appraisals:** Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the *F508del* mutation (2016). NICE Technology appraisal guidance 398. Review date in line with interim data collection agreement. Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (2013). NICE Technology appraisal guidance 276. Review date to be confirmed. Mannitol dry powder for inhalation for treating cystic fibrosis (2012). NICE Technology appraisal guidance 266. Review date to be confirmed. **Related Guidelines:** Cystic fibrosis: diagnosis and management (2017). NICE guideline 78. Reviewed October 2021. **Related Quality Standards:** Cystic Fibrosis (2018). NICE quality standard 168.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 45

[a] At the second committee meeting to discuss ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis, the committee concluded that ivacaftor should be included as a comparator in the F/Gating population because people with a gating mutation may be eligible for IVA if they also have an F508del mutation"

References

1. The Cystic Fibrosis Trust (2021), UK CF Registry: 2021 Annual Data Report [accessed 13 January 2023]

2. The Cystic Fibrosis Trust. What is cystic fibrosis? [accessed 29 September 2022]

3. The Cystic Fibrosis Trust. What causes cystic fibrosis? [accessed 13 January 2023]

4. NHS England (2022) Updated Commissioning Statement. Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations [accessed 13 January 2023]