NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Evaluation

Elexacaftor, tezacaftor, lumacaftor and ivacaftor for treating cystic fibrosis [ID3834]

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of elexacaftor, tezacaftor, lumacaftor and ivacaftor 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 1,400 known mutations that can cause cystic fibrosis.[1] 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 8850 (90%) people with cystic fibrosis carry at least 1 copy of the F508del mutation.

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 lung transplantation. 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 ivacaftor/tezacaftor/elexacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and ivacaftor via the NHS while further data are collected.

The technologies

Elexacaftor, tezacaftor and ivacaftor 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'.

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. It has 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'.

Interventions	• Elexacaftor, tezacaftor and ivacaftor 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

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
	• The interventions will be compared to each other

Outcomes	The outcome measures to be considered include: • mortality • forced expiratory volume • lung function • body mass index • respiratory symptoms • pulmonary exacerbations • pulmonary bacterial colonisation • frequency and severity of acute infections • need for hospitalisation and other treatments • exercise tolerance/capacity • 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 appraisals (previously referred and expected to be included in the MTA):** Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation. NICE technology appraisal guidance [ID1303]. Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation [ID1661]. Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years old homozygous for the F508del mutation [ID1486]. **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

Questions for consultation

Where do you consider these technologies will fit into the existing care pathway for treating cystic fibrosis?

What is established clinical management for cystic fibrosis in the NHS?

Do you consider that the use of these technologies could result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments are licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

References

1. The Cystic Fibrosis Trust (2021), UK CF Registry: 2020 Annual Data Report [accessed 29 September 2022]

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