NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of elexacaftor in combination with tezacaftor and ivacaftor within its marketing authorisation for treating cystic fibrosis in people with at least one F508del mutation.

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 over 10,000 people in the UK and has an incidence of 1 in 2500 live births. About 1 in 25 people are carriers of a faulty gene (or 'mutation') that can cause cystic fibrosis[1]. There are over 1000 known mutations that can cause cystic fibrosis. 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.

In October 2019, NHS England & Improvement announced they and Vertex have concluded an access agreement to enable eligible patients in England access to treatment with ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor via the NHS.

The technology

Elexacaftor, tezacaftor and ivacaftor combination therapy (brand name unknown, Vertex Pharmaceuticals) is a systemic protein modulator. Elexacaftor and tezacaftor are correctors of the cystic fibrosis transmembrane conductance regulator (CFTR) and ivacaftor is a potentiator of the CFTR. Elexacaftor, tezacaftor and ivacaftor are orally administered once daily as a fixed-dose combination product in the morning, along with ivacaftor administered alone once daily in the evening.

Elexacaftor, tezacaftor and ivacaftor combination therapy does not currently have a marketing authorisation in the UK for treating cystic fibrosis. It has been studied in clinical trials compared with triple placebo, tezacaftor and ivacaftor combination in people aged 12 years and older with cystic fibrosis with at least one F508del mutation[4, 5].

Intervention(s)	Elexacaftor, tezacaftor and ivacaftor combination therapy, followed by ivacaftor monotherapy
Population(s)	People aged 12 years and above with cystic fibrosis with at least one F508del mutation
Comparators	Established clinical management without elexacaftor, tezacaftor and ivacaftor combination therapy (such as, best supportive care including but not limited to, mannitol dry powder for inhalation, inhaled mucolytics, nebulised hypertonic saline, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes, and oral, nebulised and intravenous antibiotics)
Outcomes	The outcome measures to be considered include: • mortality • lung function • body mass index • respiratory symptoms • pulmonary exacerbations • frequency and severity of acute infections • need for hospitalisation and other treatments • 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.
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 and NICE Pathways	Related Technology Appraisals: 'Lumacaftor and ivacaftor for treating cystic fibrosis homozygous for the F508del mutation' (2016) NICE Technology Appraisal 398. 'Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis' (2013) NICE Technology Appraisal 276. Static list. 'Mannitol dry powder for inhalation for treating cystic fibrosis' (2012) NICE Technology Appraisal 266. Static list. Related guidelines (including guidelines in development): 'Cystic fibrosis: diagnosis and management of cystic fibrosis' (2017). 'Cystic fibrosis' NICE quality standard. Publication expected May 2018 NICE advice: 'Cystic fibrosis: long-term azithromycin'. NICE advice ESUOM37. Related NICE Pathways: Respiratory conditions (2015) NICE pathway. http://pathways.nice.org.uk/

	Data collection agreement - ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor (2019)
Related National Policy	NHS England (2015) Cystic fibrosis – adults. Service specifications Reference A01/S/a NHS England (2015) Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis (named mutations) Reference A01/P/c NHS England (2014) Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis Reference A01/P/b NHS England (2016) Clinical Commissioning Policy: Continuous aztreonam lysine for cystic fibrosis (all ages) Reference 16001/P Manual for prescribed specialised services, May 2016, 'Section 45: Cystic fibrosis services (adults and children)'. NHS England. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2, 4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Is the population listed appropriate?

Have all relevant comparators for elexacaftor in combination with tezacaftor and ivacaftor been included in the scope for the population?

- Which treatments are considered to be established clinical practice in the NHS for cystic fibrosis with a F508del mutation?
- How should best supportive care be defined?
- Do you agree that this appraisal should focus on elexacaftor in combination with tezacaftor and ivacaftor compared with best supportive care? And therefore not on the comparison with tezacaftor/ivacaftor or lumacaftor/ivacaftor, because these combinations have either not been appraised or recommended by NICE for routine use in the NHS in England?
  If not
- Should tezacaftor/ivacaftor be included as a comparator?
- Should lumacaftor/ivacaftor be included as a comparator?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom elexacaftor in combination with tezacaftor and ivacaftor is expected to be more clinically effective and cost effective or other groups that should be examined separately?

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 elexacaftor in combination with tezacaftor and ivacaftor will be 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.

Do you consider elexacaftor in combination with tezacaftor and ivacaftor to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of elexacaftor in combination with tezacaftor and ivacaftor can result in any potential significant and 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 Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. The Cystic Fibrosis Trust (2019), UK CF Registry: 2018 annual data report [accessed 06 December 2019]

2. Cystic Fibrosis Medicine. The genetics of cystic fibrosis. http://www.cfmedicine.com/cfdocs/cftext/genetics.htm. [accessed 06 December 2019]

3. Allison Peebles *et al.* 2005. Cystic fibrosis care: a practical guide. Elsevier ISBN 0 443 10003 9.

4. Heijerman et al, VX17-445-103 Trial Group. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1940-1948. doi: 10.1016/S0140-6736(19)32597-8. Epub 2019 Oct 31.

5. Keating et al, VX16-445-001 Study Group. VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. N Engl J Med. 2018 Oct 25;379(17):1612-1620. doi: 10.1056/NEJMoa1807120. Epub 2018 Oct 18.

