NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of tezacaftor in combination with ivacaftor within its marketing authorisation for treating cystic fibrosis in people with the 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 8700 (90%) people with cystic fibrosis carry at least 1 copy of the F508del mutation.

There are currently no treatment options available in the NHS that specifically target F508del mutations in the CFTR gene. 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.

The technology

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

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 placebo, tezacaftor or ivacaftor alone in people aged 12 years and older with cystic fibrosis who are homozygous or heterozygous for the F508del mutation[4, 5].

Intervention(s)	Tezacaftor and ivacaftor combination therapy, followed by ivacaftor monotherapy
Population(s)	People with cystic fibrosis who are either: • homozygous for the F508del mutation, or • heterozygous for the F508del mutation and a residual function mutation
Comparators	Established clinical management without 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/
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

References

1. The Cystic Fibrosis Trust (2017), UK CF Registry: 2016 annual data report [accessed 16 January 2018]

2. Cystic Fibrosis Medicine. The genetics of cystic fibrosis. http://www.cfmedicine.com/cfdocs/cftext/genetics.htm Accessed 12 April 2016.

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

4. Taylor-Cousar et al, Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508delN Engl J Med 2017; 377:2013-2023 November 23, 2017DOI: 10.1056/NEJMoa1709846

5. Rowe et al, Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis N Engl J Med 2017; 377:2024-2035 November 23, 2017DOI: 10.1056/NEJMoa1709847