NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lumacaftor and ivacaftor combination therapy for treating cystic fibrosis homozygous for the F508del mutation

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of lumacaftor in combination with ivacaftor within its marketing authorisation for treating cystic fibrosis in people who are homozygous for 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 defective, it leads 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 children and young adults 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. For someone to be born with cystic fibrosis, they must inherit a faulty gene from both parents. There are over 1000 known mutations that can cause cystic fibrosis. The most common mutation is the F508del mutation and around 40–50% of people with cystic fibrosis carry 2 copies of the F508del mutation (termed 'homozygous').

There are currently no treatment options available that specifically target 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 guidance 266 recommends mannitol dry powder for inhalation as an option for treating cystic fibrosis in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and, whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate.

The technology

Lumacaftor and ivacaftor combination therapy (Orkambi, Vertex Pharmaceuticals) is a systemic protein modulator. Lumacaftor is a corrector of the cystic fibrosis transmembrane conductance regulator (CFTR) and ivacaftor is a potentiator of the CFTR. It is orally administered as a fixed-dose combination product.

Lumacaftor 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 in people aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation.

Intervention(s)	Lumacaftor and ivacaftor combination therapy
Population(s)	People with cystic fibrosis who are homozygous for the F508del mutation
Comparators	Established clinical management without lumacaftor 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: Technology Appraisal No. 266, November 2012, 'Mannitol dry powder for inhalation for treating cystic fibrosis'. Review Proposal Date October 2015. Technology Appraisal No. 276, March 2013, 'Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis'. Review Proposal Date December 2015. Related Guidelines: Clinical Guideline in Preparation, 'Cystic fibrosis: diagnosis and management of cystic fibrosis'. Earliest anticipated date of publication February 2017.
Related National Policy	Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf Manual for prescribed specialised services, November 2014, 'Section 45: Cystic fibrosis services (all ages)'. NHS England. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf