

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

**Lumacaftor in combination with ivacaftor for treating cystic fibrosis
homozygous for the F508del mutation**

Draft scope (pre-referral)

Draft 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. Although cystic fibrosis is a progressive condition that limits life expectancy, it has an improving prognosis.

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 the cystic fibrosis gene. For someone to be born with cystic fibrosis, both parents must carry the defective gene. There are over 1000 known mutations of the cystic fibrosis gene. The most common mutation is the F508del mutation and around 52% of people with cystic fibrosis are homozygous for the F508del mutation.

There are currently no treatment options available that specifically target the F508del mutation. Current treatments for cystic fibrosis generally manage the 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 in combination with ivacaftor (brand name unknown, Vertex Pharmaceuticals) is an 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.

Lumacaftor in combination with ivacaftor 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 in combination with ivacaftor
Population(s)	People with cystic fibrosis who are homozygous for the F508del mutation
Comparators	Established clinical management without lumacaftor in combination with ivacaftor (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 and pancreatic enzymes)
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • mortality • lung function • body mass index • respiratory symptoms • frequency and severity of acute infections • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>

Other considerations	<p>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.</p> <p>If the evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.</p>
Related NICE recommendations and NICE Pathways	<p>Related Technology Appraisals:</p> <p>Technology Appraisal No. 266, November 2012, 'Mannitol dry powder for inhalation for treating cystic fibrosis'. Review Proposal Date October 2015.</p> <p>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.</p> <p>Related Guidelines:</p> <p>Clinical Guideline in Preparation, 'Cystic fibrosis: diagnosis and management of cystic fibrosis'. Earliest anticipated date of publication February 2017.</p>
Related National Policy	<p>Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 2 and 4. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf</p> <p>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</p>

Questions for consultation

Are there likely to be any stopping criteria assessed in clinical practice for lumacaftor in combination with ivacaftor?

Have all relevant comparators for lumacaftor in combination with ivacaftor been included in the scope? Which treatments are considered to be established clinical practice in the NHS for people with cystic fibrosis who are homozygous for the F508del mutation? How should best supportive care be defined?

Is the subgroup suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom lumacaftor in combination with 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 lumacaftor in combination with 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 lumacaftor in combination with 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 lumacaftor in combination with 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.

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>)