NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years old 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 children ages 2 to 11 years old 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 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.[1,2] About 1 in 25 people are carriers of a faulty gene (or 'mutation') that can cause cystic fibrosis.[2] There are over 1000 known mutations that can cause cystic fibrosis.[2] 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. In 2015, 1,227 children aged under 11 with homozygous F508del mutations were admitted to centres in England.[3]

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, mannitol dry powder for inhalation 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 276 recommends colistimethate sodium and tobramycin dry powders for inhalation for treating chronic lung infections in some people with cystic fibrosis.

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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 combination tablet.

Lumacaftor and ivacaftor combination therapy has a marketing authorisation in the UK for treating cystic fibrosis in people aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.

Lumacaftor and ivacaftor combination therapy does not have a marketing authorisation in the UK for treating cystic fibrosis in children aged 2 to 5 years old. It has been studied in clinical trials in children aged 2 to 5 years old who who are homozygous for the F508del mutation in the CFTR gene.

NICE technology appraisal guidance 378 does not recommend lumacaftor and ivacaftor combination therapy for treating cystic fibrosis in people aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Intervention(s)	Lumacaftor with ivacaftor
Population(s)	Children ages 2 to 11 years old 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.

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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–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (2016) NICE technology appraisal guidance 398 'Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (2013) NICE technology appraisal guidance 276. Static list. **Appraisals in development (including suspended appraisals)** Suspended Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation [ID1303] NICE technology appraisal guidance. **Related Guidelines:** Cystic fibrosis: diagnosis and management (2017) NICE guideline NG78 **Related Quality Standards:** Cystic fibrosis (2018) NICE quality standard 168 Related NICE Pathways:

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	Cystic fibrosis (2017, updated 2018) NICE pathway
Related National Policy	NHS England (2015) Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis (named mutations) Reference A01/P/c NHS England (2015) Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis NHS England (2015) Service specification: A01/S/b Cystic Fibrosis (Children) NHS England (2017) Manual for Prescribed Specialised Services 2017/18. https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.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

Have all relevant comparators for lumacaftor with ivacaftor been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for cystic fibrosis?

How should best supportive care be defined? How does best supportive care differ from patients aged 12 years and older? Does best supportive care differ for patients aged between 2 and 5 years old and patients aged between 6 and 12 years old?

Is the dosing regimen for lumacaftor with ivacaftor expected to be different for younger patients?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate?

Are there any other subgroups of people in whom lumacaftor with ivacaftor is expected to be more clinically effective and cost effective or other groups that should be examined separately?

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Where do you consider lumacaftor with ivacaftor will fit into the existing NICE pathway, cystic fibrosis?

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 with ivacaftor is 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 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 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.

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).

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References

1. The Cystic Fibrosis Trust (2017), UK CF Registry: 2016 annual data report. Available athttps://www.cysticfibrosis.org.uk/~/media/documents/the-work-we-do/uk-cf-registry/uk-cf-registry-annual-data-report-2016.ashx?la=en [accessed July 2018]

2. Cystic Fibrosis Medicine. The genetics of cystic fibrosis. Available at http:/www.cfmedicine.com/cfdocs/cftext/genetics.htm [accessed July 2018].

3. The Cystic Fibrosis Trust (2015), UK CF Registry: Genotype data by nation and age. Available at https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources [accessed July 2018]

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