

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Proposed Health Technology Appraisal**

**Tezacaftor and ivacaftor 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 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<sup>1</sup>. 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 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 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 are 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.

<b>Intervention(s)</b>	Tezacaftor and ivacaftor combination therapy, followed by ivacaftor monotherapy
<b>Population(s)</b>	People with cystic fibrosis who are either: <ul style="list-style-type: none"> <li>• homozygous for the F508del mutation, or</li> <li>• heterozygous for the F508del mutation</li> </ul>
<b>Comparators</b>	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)
<b>Outcomes</b>	The outcome measures to be considered include: <ul style="list-style-type: none"> <li>• mortality</li> <li>• lung function</li> <li>• body mass index</li> <li>• respiratory symptoms</li> <li>• pulmonary exacerbations</li> <li>• frequency and severity of acute infections</li> <li>• need for hospitalisation and other treatments</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<b>Economic analysis</b>	<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>
<b>Other considerations</b>	<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 evidence allows, the appraisal will consider the relationship between baseline lung function and clinical effectiveness.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p>Related Technology Appraisals:</p> <p>‘Lumacaftor and ivacaftor for treating cystic fibrosis homozygous for the F508del mutation’ (2016) NICE Technology Appraisal 398.</p> <p>‘Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis’ (2013) NICE Technology Appraisal 276. Static list.</p> <p>‘Mannitol dry powder for inhalation for treating cystic fibrosis’ (2012) NICE Technology Appraisal 266. Static list.</p> <p>Guidelines in development:</p> <p>‘Cystic fibrosis: diagnosis and management of cystic fibrosis’. Publication expected October 2017.</p> <p>‘Cystic fibrosis’ NICE quality standard. Publication expected May 2018</p> <p>NICE advice:</p> <p>‘Cystic fibrosis: long-term azithromycin’. NICE advice ESUOM37.</p> <p>Related NICE Pathways:</p> <p>Respiratory conditions (2015) NICE pathway.  <a href="http://pathways.nice.org.uk/">http://pathways.nice.org.uk/</a></p>

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

Are the two populations listed appropriate? Is tezacaftor-ivacaftor expected to be used for both homozygous and heterozygous F508del CFTR mutation?

Have all relevant comparators for tezacaftor in combination with ivacaftor been included in the scope for both populations? Which treatments are considered to be established clinical practice in the NHS for cystic fibrosis homozygous or heterozygous for the F508del mutation?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom tezacaftor 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 tezacaftor 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 tezacaftor 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 tezacaftor 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.

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. Cystic Fibrosis Trust (2016) [UK cystic fibrosis registry: 2015 annual data report](#) [accessed 8 August 2017]

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.