

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Proposed Health Technology Appraisal**

**Human alpha1-proteinase inhibitor for treating emphysema**

**Draft scope (pre-referral)**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of human alpha1-proteinase inhibitor within its marketing authorisation for treating emphysema.

**Background**

Emphysema is a chronic lung disease in which the air sacs in the lungs become larger than normal and the walls of the air sacs are damaged. Emphysema is one of a group of conditions collectively known as chronic obstructive pulmonary disease (COPD). COPD is a slowly progressive condition characterised by airflow limitation that is not fully reversible. The symptoms include coughing, wheezing, breathlessness, and frequent chest infections. Exacerbations often occur, where there is a rapid and sustained worsening of symptoms. An estimated 900,000 people in the UK have been diagnosed with COPD and an additional 2 million people have undiagnosed COPD.

Alpha1-antitrypsin is a protein made in the liver that circulates in blood plasma. It protects the lungs from damage by enzymes such as neutrophil elastase. Some people have a genetic mutation that causes them to have low levels of alpha1-antitrypsin. This deficiency can mean that neutrophil elastase damages cells in the lungs, causing emphysema. People with alpha1-antitrypsin deficiency who smoke can have COPD symptoms in their 20s, whereas people with alpha1-antitrypsin deficiency who have never smoked are more likely to have symptoms over the age of 40.

Between 1 in 1600 and 1 in 5000 newborn babies have alpha1-antitrypsin deficiency, but not all will develop emphysema.<sup>1</sup> Based on a disease registry in the West Midlands, it is estimated that 670 people in England have emphysema caused by alpha1-antitrypsin deficiency.<sup>1</sup> About 540 of these people (80%) will have clinically significant emphysema that requires treatment. However, the true number of people affected may be higher because many people have undiagnosed COPD. Moreover, some people with COPD have undiagnosed alpha1-antitrypsin deficiency.<sup>2</sup>

Currently, the treatment for emphysema is the same regardless of whether people have alpha1-antitrypsin deficiency. NICE clinical guideline 101 recommends that people with COPD should be provided with help to stop smoking and should be offered pneumococcal vaccination and an annual influenza vaccination. NICE clinical guideline 101 recommends initial treatment with short-acting bronchodilators. For people who remain breathless

or have exacerbations despite using short-acting bronchodilators as required, NICE clinical guideline 101 recommends a sequence of inhaled treatments. These treatments may include a long-acting beta2 agonist (LABA), a long-acting muscarinic antagonist (LAMA) or inhaled corticosteroids, alone or in combination. Some people may have oral therapy with slow-release theophylline or a mucolytic. Additional treatment options include pulmonary rehabilitation (a multidisciplinary programme of care), oxygen therapy and, for those with severe disease, lung transplantation.

Replacement therapy (also known as augmentation therapy) aims to boost the levels of alpha-1 antitrypsin in the blood. It involves an intravenous infusion of alpha1-proteinase inhibitor derived from the blood plasma of healthy donors. NICE clinical guideline 101 does not recommend replacement therapy for people with alpha1-antitrypsin deficiency and COPD.

### The technology

Human alpha1-proteinase inhibitor (Respreeza, CSL Behring) inhibits neutrophil elastase and other proteases in the lower respiratory tract to slow the underlying destruction of lung tissue. It is administered by intravenous infusion.

The Committee for Medicinal Products for Human Use has recommended that a marketing authorisation should be granted for this technology. Human alpha1-proteinase inhibitor will be indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (such as genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ).

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| <b>Intervention(s)</b> | Human alpha1-proteinase inhibitor   |
| <b>Population(s)</b>   | Adults with emphysema and severe alpha1-antitrypsin deficiency  |
| <b>Comparators</b>     | <p>Established clinical management without alpha1-antitrypsin, which may include but is not restricted to:</p> <ul style="list-style-type: none"> <li>• short-acting bronchodilators</li> <li>• long-acting beta2 agonists (LABA)</li> <li>• long-acting muscarinic antagonists (LAMA)</li> <li>• inhaled corticosteroids</li> <li>• oral therapy with slow-release theophylline or a mucolytic</li> <li>• pulmonary rehabilitation</li> <li>• oxygen therapy</li> <li>• lung transplantation.</li> </ul> |

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| <b>Outcomes</b>                                       | <p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• lung function</li> <li>• incidence and severity of acute exacerbations, including hospitalisation</li> <li>• symptom control (e.g. shortness of breath)</li> <li>• mortality</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>The appraisal will include consideration of the costs and implications of genetic testing, but will not make recommendations on specific diagnostic tests or devices.</p> <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>  |
| <b>Related NICE recommendations and NICE Pathways</b> | <p>Related Technology Appraisals:</p> <p>Roflumilast for the management of severe chronic obstructive pulmonary disease (2012). NICE Technology Appraisal 244. Review date TBC. <i>Note: this guidance covers COPD associated with chronic bronchitis only.</i></p> <p>Related Guidelines:</p> <p>Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (2010). NICE guideline 101. Review date June 2016.</p> <p>Related Interventional Procedures:</p> <p>Insertion of endobronchial valves for lung volume</p> |

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|  | <p>reduction in emphysema (2013). NICE interventional procedures guidance 465.</p> <p>Lung volume reduction surgery for advanced emphysema (2005). NICE interventional procedures guidance 114.</p> <p>Related Quality Standards:</p> <p>Chronic obstructive pulmonary disease (2011) NICE quality standard 10.</p> <p>Related NICE Pathways:</p> <p>Chronic obstructive pulmonary disease NICE pathway <a href="http://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease">http://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease</a></p> |
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| <b>Related National Policy</b> | <p>NHS England: Manual for prescribed specialised services 2013/14. Chapter 4.<br/> <a href="http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf">http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf</a></p> <p>Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 2, 4 and 5.<br/> <a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf</a></p> |
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### Questions for consultation

Questions on diagnosis and genetic testing:

- For people diagnosed with COPD, is it part of established NHS practice to measure alpha1-antitrypsin levels?
- How is 'deficiency' of alpha1-proteinase defined? How is 'severe deficiency' defined?
- For people with COPD and low levels of alpha1-antitrypsin, is it part of established NHS practice to test for mutations of the SERPINA1 gene that may cause the deficiency? Which alleles of the SERPINA1 gene can be detected routinely?

How many people in England have emphysema caused by alpha1-antitrypsin deficiency and would potentially be eligible for treatment with human alpha1-proteinase inhibitor?

During treatment with human alpha1-proteinase inhibitor, is it necessary to conduct repeated tests to monitor levels of alpha1-antitrypsin in the blood?

Have all relevant comparators for human alpha1-proteinase inhibitor been included in the scope? Which treatments are considered to be established clinical practice in the NHS for emphysema?

Are there any subgroups of people in whom human alpha1-proteinase inhibitor is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider human alpha1-proteinase inhibitor will fit into the existing NICE pathway on [chronic obstructive pulmonary disease](#)?

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 human alpha1-proteinase inhibitor 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 human alpha1-proteinase inhibitor 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 human alpha1-proteinase inhibitor 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>)

### References

1. NIHR Horizon Scanning Centre, 2014. Briefing note: [Alpha-1 antitrypsin \(Respreeza\) for emphysema associated with alpha-1 antitrypsin deficiency – maintenance therapy](#)
2. Alpha-1 UK Support Group, 2015. [A healthcare professional's guide to alpha-1 antitrypsin deficiency](#).