NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Human alpha1-proteinase inhibitor for treating emphysema

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using human alpha1-proteinase inhibitor in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of human alpha1-proteinase inhibitor in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2019

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using human alpha1-proteinase inhibitor in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 9 January 2020

Third evaluation committee meeting: TBC

Details of membership of the evaluation committee are given in section **Error! Reference source not found.**.

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1 Recommendations

1.1 Human alpha1-proteinase inhibitor (A1PI) is not recommended, within its marketing authorisation, as maintenance treatment to slow the progression of emphysema in adults with severe alpha1-proteinase inhibitor deficiency.

1.2 This recommendation is not intended to affect treatment with human A1PI that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

A1PI deficiency is a rare, life-limiting condition that causes emphysema. Current treatment options treat the symptoms but not the cause of the condition. Human A1PI aims to supplement the deficient protein in people with A1PI deficiency.

Clinical trial evidence shows that human A1PI slows decline in lung density more than placebo. Human A1PI could also provide benefits in quality of life, walking distance and lung function, but this is unproven. Human A1PI is associated with a survival benefit, but there is substantial uncertainty in the available evidence and the size of this benefit is unknown.

Human A1PI could provide meaningful clinical benefits for patients and carers. But there are considerable uncertainties in the economic modelling, and the cost-effectiveness estimates for human A1PI are much higher than those NICE normally considers acceptable for highly specialised technologies. Even considering the benefits not captured by

the model, A1PI does not provide value for money within the context of a highly specialised service, and is not recommended for use in the NHS.

2 The condition

2.1 Alpha1-proteinase inhibitor (A1PI) deficiency, also known as alpha1-antitrypsin deficiency (AATD), is a rare genetic disorder. Lack of the protective protein A1PI makes people more vulnerable to body tissue damage from protease enzymes produced in response to infections and environmental toxins (such as tobacco smoke and pollution). Severe A1PI deficiency is defined by an A1PI protein concentration below 11 micromolar. Lack of A1PI can lead to emphysema – a chronic lung condition in which the walls of the air sacs in the lungs are damaged and become less able to move air in and out. Less commonly, A1PI deficiency causes liver and skin damage.

2.2 The symptoms of emphysema include coughing, wheezing, breathlessness, and frequent chest infections. Emphysema can also reduce life expectancy. The development and characteristics of A1PI deficiency vary considerably between individuals, with genetics and environmental exposure to toxins both affecting the course of the disease.

2.3 The exact prevalence and incidence of emphysema associated with A1PI deficiency is unknown. It is thought that there are about 670 people with emphysema caused by A1PI deficiency in England. A1PI treatment may be considered for about 200 to 600 people in England.

2.4 There is no cure for A1PI deficiency. The aim of treatment is to delay the progression of emphysema and manage symptoms. This provides short-term relief, but does not treat the cause of the condition. Treatment typically involves standard therapies for chronic obstructive pulmonary disease including inhaled bronchodilators, inhaled corticosteroids, oxygen therapy, and pulmonary rehabilitation. For people with progressed disease, lung transplant can be considered as an option.

3 The technology

3.1 Human alpha1-proteinase inhibitor (human A1PI; Respreeza, CSL Behring) is a treatment that aims to supplement the deficient protein in people with A1PI deficiency. Respreeza has a marketing authorisation for 'maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (for example genotypes PiZZ, PiZ [null], Pi [null,null], PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (for example lower forced expiratory volume per second [FEV1] predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency'. Respreeza is administered weekly by intravenous infusion.

3.2 The adverse reactions listed as common in Respreeza's summary of product characteristics include: dizziness, headache, dyspnoea, and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The list price of Respreeza in England is £220 per 1,000 mg vial (excluding VAT; British national formulary), equating to £57,200 per year for a person weighing 67 to 83 kg.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by CSL Behring, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Impact of A1PI deficiency

4.1 The patient experts explained that alpha1-proteinase inhibitor (A1PI) deficiency is a highly debilitating condition:

- Breathlessness regularly leaves them exhausted and affects all aspects of their day-to-day lives. Careful planning is needed to complete daily tasks when people are limited by breathlessness. Basic activities such as walking, speaking, dressing and eating become increasingly challenging as the disease progresses.
- They are constantly fearful of social interactions, because without the protective A1PI protein they are vulnerable to infection and environmental toxins. Any respiratory infection can cause more tissue damage, reducing life expectancy. People with A1PI deficiency often turn down invitations to social events to avoid travelling or exposure to toxins or infections, which leads to social isolation and affects relationships and family life.
- A1PI deficiency is often diagnosed in mid adulthood, at a time when financial and family responsibilities can be particularly important. Being physically and socially limited by A1PI deficiency can lead to reduced earning potential because people with the condition may be unable to travel or continue working.
- The physical and social effects of the condition contribute to its significant impact on mental health and emotional wellbeing. Uncertainty about future health also causes substantial anxiety.
- As A1PI deficiency progresses people lose their independence and increasingly rely on help from family members and carers. This affects carers of people with A1PI deficiency emotionally, physically and financially.

The committee understood that A1PI deficiency severely affects people's ability to do normal tasks and they may significantly change or limit their behaviour to reduce the risk of lung damage. It concluded that A1PI

deficiency has significant physical and emotional effects on people with the condition and their families.

Current treatment options

4.2 Current treatment options for emphysema associated with A1PI deficiency are based on standard therapies for chronic obstructive pulmonary disease (see section 2.4). The committee recognised that these options treat the symptoms of A1PI deficiency, to an extent, but do not treat the cause of the condition. The patient experts noted that current treatments do not protect against future lung damage. The committee recalled that people with A1PI deficiency may alter their behaviour to avoid lung damage (see section 4.1), and recognised that the lack of protection provided by current treatments would contribute to this. The committee understood that oxygen therapy is offered as a treatment option for some people with A1PI deficiency (see section 2.4), but it is restrictive and embarrassing. The patient experts noted that careful planning is needed to ensure sufficient oxygen supply, highlighting that this causes substantial anxiety. The committee understood that lung transplant was considered as a last resort for people with progressed disease. A clinical expert explained that there were significant risks associated with such invasive surgery. The clinical experts were aware of the high risk of mortality associated with the surgery and after transplant, and that complications and ongoing health problems after surgery can be severe. The patient experts commented that lung transplant was a frightening prospect but can be appropriate for some people with A1PI deficiency, at the right point in the treatment pathway. The committee understood that not all people with progressed disease would have a lung transplant, for reasons including individual choice, transplant eligibility and limited availability of organs. The committee recognised that the risks associated with lung transplant make the decision to have the surgery challenging, although it is an important part of the treatment pathway for some people. It concluded that there was an unmet need for an effective treatment for A1PI deficiency in the NHS.

Impact of the new technology

Patient and clinical perspectives

4.3 The patient experts explained that an important benefit of A1PI therapy would be the knowledge that there is protection from further tissue damage, and that this benefit would be substantial. They described the experiences of people with A1PI deficiency who had human A1PI treatment, highlighting that it allowed people to return to their usual activities and socialise again. The clinical experts noted that human A1PI could slow the progression of emphysema, potentially delaying the need for lung transplant. The committee recalled the patient experts' comment that lung transplant was a frightening prospect (see section 4.2), and recognised that avoiding surgery would be considered an important benefit for people with A1PI deficiency. The committee concluded that human A1PI had potential to protect people with A1PI deficiency from future tissue damage, and agreed that this could lead to a positive change in their behaviour. It further concluded that avoiding lung transplant could reduce some of the anxiety experienced by people with A1PI deficiency.

Use in clinical practice

4.4 The committee noted the marketing authorisation for human A1PI (Respreeza) stipulates that people must have progressive lung disease (for example, lower forced expiratory volume in 1 second, percent predicted [FEV1% predicted], impaired walking capacity or increased number of exacerbations). It judged that progressive lung disease was not fully defined in the marketing authorisation, and therefore it would need to consider how the decision to start treatment would be made in practice. The clinical experts noted that they would use their clinical judgement in deciding to offer treatment with human A1PI. One clinical expert explained that the presence of emphysema on a CT scan shows the patient is susceptible to developing lung damage and would have the potential to benefit from treatment. The clinical experts acknowledged the potential value of defined starting criteria, and considered measures of disease

progression and lung deterioration. They noted that CT lung densitometry could be the most appropriate method to assess the progression of emphysema, because spirometry measures (such as measurement of FEV1) were not as reliable. During consultation the company submitted clinical trial evidence exploring the relationship between the rate of lung density decline before treatment and the treatment benefit. The results from the analyses are considered academic in confidence by the company, so cannot be reported here. The committee was aware that monitoring disease progression would need several years of observation before treatment could start (particularly if using spirometry), and noted the concerns from patient experts about having to wait such a long time for treatment while lung damage becomes irreparable and the immediate treatment benefits are missed. The committee recognised that it may be valuable in clinical practice to agree appropriate starting criteria. However, it concluded that it was not able to recommend specific starting criteria or make a recommendation for human A1PI in a specific group.

4.5 The committee asked the clinical experts when people with A1PI deficiency would stop treatment with human A1PI, and whether treatment would be stopped if there was no benefit. The clinical experts recognised the potential value of such an approach, but explained that it would be challenging to objectively identify defined benefits in individual patients in practice, so they would be likely to continue until lung transplant or death. The committee concluded that it was unlikely to be possible to define stopping rules for human A1PI, and therefore lifelong treatment would be expected.

Clinical effectiveness evidence

4.6 The committee discussed the clinical trial evidence available for human A1PI:

- RAPID (n=180), a randomised controlled trial, assessing the efficacy and safety of human A1PI (n=93) compared with placebo (n=87) for up to 24 months in adults aged 18 to 64 diagnosed with emphysema

resulting from A1PI deficiency who had an FEV1 between 35% and 70% predicted.

- RAPID-OLE (n=140), a single-arm open label extension study, which included people from RAPID and compared the efficacy and safety of longer-term A1PI in people who had treatment with human A1PI in RAPID (early starters) with people who switched from placebo to human A1PI (late starters).

4.7 There was a difference of 3.2 grams/litre in baseline lung density between groups in RAPID. The ERG considered that this difference may be important, taking into account estimates of the minimal clinically important differences for lung density that have been published and proposed (for example, 2.89 grams/litre). The clinical experts explained that this baseline difference was not a concern, and noted that other baseline characteristics were well balanced. The company stated that it had done a covariate-adjusted analysis, which showed that the treatment effect of human A1PI was consistent even when differences in baseline lung density were adjusted for. The committee concluded that it would bear in mind the baseline differences between RAPID treatment groups when interpreting the clinical results.

4.8 The company also submitted clinical effectiveness evidence from systematic literature reviews, meta-analyses and observational studies. A meta-analysis by Edgar et al. (2017) compared human A1PI with placebo across various outcomes. An updated meta-analysis by Chapman et al. (2009) compared the effectiveness of human A1PI with placebo, stratified by categories of FEV1% predicted. Survival data from a US registry, AlphaNet (a US non-profit, patient-run health management company that coordinates services for people with A1PI deficiency) and from the UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) were also considered.

4.9 The committee discussed the observational evidence. It was aware that ADAPT had been running for over 20 years. The clinical experts explained

that the programme was based at a single study site but collected data from patients across the UK. During consultation, stakeholders highlighted that enrolment in the programme could be prone to bias. The patient experts explained that not all patients want to take part in research and the programme may exclude people who are not able to travel to the study site because of physical, financial or geographical constraints. The patient experts were concerned that the ADAPT data may not accurately reflect the population of people with A1PI deficiency in England. The clinical experts agreed that the ADAPT population was likely to have a lower burden of disease than the population for whom A1PI treatment would be an option in NHS clinical practice in England. The committee recognised that ADAPT provided relevant observational evidence but concluded that it had potentially important limitations.

Clinical trial results

4.10 The committee discussed the lung density results:

- RAPID: at 24 months there was a reduction in lung density decline at total lung capacity in people who had human A1PI (−1.45 grams/litre/year) compared to those who had placebo (−2.19 grams/litre/year)
- RAPID-OLE: at 48 months the rate of lung density decline was further reduced in the early starter group (−1.08 grams/litre/year). People switching from placebo to human A1PI (late starters) had a reduction in lung density decline (−1.31 grams/litre/year).

The committee noted that there was a statistically significant reduction in lung density decline for people who had human A1PI compared with placebo. It also noted that the treatment effect was sustained in the early starters in RAPID-OLE, and that late starters had a reduction in decline after switching from placebo to human A1PI. The clinical experts highlighted that the improvements in lung density decline seen in the RAPID studies would be important to patients. The committee noted that consistent findings were seen in the Edgar et al. meta-analysis, which

included the RAPID studies and 2 other studies comparing human A1PI with placebo. The committee concluded that human A1PI slows the rate of lung density decline and agreed that this was an important measurable benefit.

4.11 The committee discussed the secondary outcomes from the RAPID trial (including lung function and walking distance). It noted that there was a greater decline in lung function (FEV1% predicted and diffusing capacity of the lungs for carbon monoxide [D_{LCO}]) for people who had human A1PI than for those who had placebo but recognised that the difference was not statistically significant. The clinical experts explained that the size of the difference in effect would not be considered clinically significant. The committee also noted that there was a greater improvement in walking distance (using the incremental shuttle walk test) for people on placebo but again recognised that the difference was not statistically significant. The committee was aware that RAPID was not powered to detect changes in lung function or walking distance, but noted that the trial showed no evidence of a beneficial treatment effect in these outcomes. The company explained that it had not been possible to power for secondary outcomes in the clinical trials because of the number of patients and the time needed to detect a treatment effect. The committee noted that the results from the updated Chapman et al. meta-analysis showed that human A1PI reduced measured lung function decline compared with no treatment in people with FEV1% predicted less than 65%. However, in people with FEV1% predicted over 65% there did not appear to be a benefit to treatment. The committee also noted that there was some evidence for long-term correlations between rate of lung density decline and declines in lung function in other studies. The committee recognised that it was biologically plausible that A1PI would improve secondary outcomes such as lung function but this was unproven.

4.12 The committee also considered data on quality of life (St George's Respiratory Questionnaire). The committee noted that in the symptom and

activity domains of the questionnaire there appeared to be an improvement for people on human A1PI treatment, but in the impact domain the results favoured placebo. The committee recognised that the differences in quality of life were not statistically significant. The patient experts explained that people who have had A1PI treatment described rapid and substantial improvements in quality of life. The committee recognised that A1PI treatment aims to prevent further damage and decline, but also there were plausible mechanisms by which it could immediately improve quality of life, such as by reducing inflammation. The committee also recalled its earlier conclusion that A1PI treatment could lead to a positive change in the behaviour of people with A1PI deficiency. The committee concluded that, although the clinical trial results were inconclusive, testimonies from clinical and patient experts showed that it was likely that A1PI would improve quality of life.

4.13 The committee noted some qualitative evidence that had been submitted by stakeholders during consultation, including interviews with patients who had had A1PI treatment. It recognised the value of this evidence along with the testimonies from clinical and patient experts. The committee acknowledged that there is widespread experience with A1PI worldwide but noted that the evidence had not been collected systematically. The committee concluded that collecting such evidence systematically would allow it to further understand the benefits of A1PI treatment for people with the condition and their families, including its effects on quality of life.

4.14 The committee noted that meta-analysis results from Edgar et al. showed a statistically significant increase in the number of pulmonary exacerbations in people who had human A1PI. The committee recognised that this would not be expected from its mechanism of action. The clinical experts explained that definitions of pulmonary exacerbations vary and can be subjective. During consultation, the company compared the RAPID study outcomes with the outcomes of other studies. This showed a lower rate of exacerbations in both RAPID treatment groups than in other studies. The committee recognised that there are challenges in comparing

exacerbation rates between studies, but this would not explain the between-group differences in RAPID. The committee expressed concern that the results from RAPID showed that human A1PI may be associated with an increased risk of pulmonary exacerbations, but the clinical experts explained that the difference was not clinically significant. The committee recognised a potential concern that A1PI may be associated with an increased risk of pulmonary exacerbations but acknowledged that this may not be a clinically important finding.

4.15 The committee considered whether there was any survival benefit associated with human A1PI. It understood that, because of the size and duration of the RAPID studies, it was not possible to draw conclusions about survival from these data. The committee considered US survival data from the Alpha-1-Antitrypsin Deficiency Registry Study Group (1998). It noted that people who were taking, or had previously taken, human A1PI had a higher probability of survival than those who had not. During consultation the company submitted evidence comparing outcomes of people who had A1PI treatment in the US as part of AlphaNet and matched people in the UK who had best supportive care as part of ADAPT. The data were used to estimate the effect of A1PI on mortality in people with A1PI deficiency. After consultation a clinical expert submitted an updated analysis, which aimed to improve comparability by excluding asymptomatic people from the ADAPT cohort. Results of both analyses are considered confidential and therefore cannot be reported here. The ERG noted that the data for people who had treatment and people who had best supportive care came from different sources, but with no other data sources in the UK this was a reasonable approach. The committee recalled the limitations of the observational evidence from ADAPT (see section 4.9). It was aware that ADAPT was used in both survival analyses, but it was not presented with evidence to resolve these limitations. The committee acknowledged that people with lower burden of disease (as in ADAPT, see section 4.9) may live longer than those with more severe disease. The committee was therefore not convinced that the size of the

survival benefit shown in the comparison would be generalisable to the expected outcome in England. It concluded that human A1PI improves survival, but based on the evidence available, the exact size of the survival benefit is unknown and may be underestimated.

Cost to the NHS and value for money

Economic model

4.16 The company presented an economic model comparing human A1PI with best supportive care. This was based on a state transition model that included 11 health states. Health states were defined according to both FEV1% predicted (below 30%, 30% to 50%, and above 50%) and lung density decline (no decline [less than 0 grams/litre/year], slow decline [0 to 2 grams/litre/year], and rapid decline [over 2 grams/litre/year]), with 2 additional health states for lung transplant. The company explained that although lung density decline is the most appropriate measure of disease progression, links between this measure and other health and cost outcomes have not yet been established. It was therefore necessary to include FEV1% predicted states to fully capture health and economic outcomes. The committee discussed whether the model structure captured the progression of emphysema associated with A1PI deficiency. A clinical expert explained that the model health states captured important and recognisable points in the progression of A1PI deficiency. During consultation stakeholders expressed concern that the health states were unnecessarily complicated and may not represent the natural disease progression of emphysema caused by A1PI deficiency. The committee considered that it was counterintuitive that the model was based on lung density decline but did not consider absolute level of lung density. The clinical experts explained that both absolute lung density and the rate of lung density decline would affect healthcare costs. The committee recognised that it was challenging to accurately model the course of A1PI deficiency, but was not fully convinced that the current model structure reliably reflected the progression of the disease. However, it concluded

that, taking into account the available evidence to link FEV1% predicted and lung density decline to health and economic outcomes, the company's rationale was logical and the model could be considered for decision making.

4.17 The committee considered the thresholds of lung density decline that defined no, slow and rapid decline in the economic model. It was aware that clinically established thresholds for the rate of lung density decline are yet to be determined. The clinical experts stated that a decline in lung density of 2 grams/litre/year (model definition of rapid decline) was consistent with a clinically meaningful change in lung density. The committee acknowledged that the model would capture important changes in lung density decline, but was not convinced that the cut-offs used in the model to define slow and rapid decline were sufficiently validated. The committee understood that the model health states were linked to health and economic outcomes, and that altering health state definitions would affect the modelled accrual of costs and benefits. The committee concluded that the definitions used to categorise lung density decline in the model lacked validation, and agreed that further validation could reduce some of its concerns about the modelling of lung density decline.

4.18 The committee considered the population included in the company's economic model. The model assumed that everyone starts in one of the lung density decline states with FEV1% predicted 30% to 50%, or over 50%. The committee recalled that it was not able to recommend specific starting criteria for A1PI treatment (see section 4.4). It agreed that the population in the model should be in line with the marketing authorisation and clinical practice. That is, it is appropriate that no more restrictive starting criteria were implemented in the economic model. The ERG removed a stopping rule from the economic model that stopped A1PI treatment when FEV1% predicted fell below 30%. The company acknowledged that including this stopping rule was an error. The committee recalled that lifelong treatment with human A1PI would be

expected (see section 4.5) and agreed that the ERG's amendment was appropriate. The committee concluded that modelling the population without specific starting criteria and removing the stopping criteria (that is, assuming lifelong treatment with A1PI) were appropriate.

Transition probabilities

4.19 To model transitions between the health states, the company used data from RAPID, ADAPT, and the updated Chapman et al. meta-analysis (see section 4.6 and 4.8). Transition probabilities between the FEV1% predicted categories and the lung density decline categories were derived independently. The ERG had some concerns, including:

- FEV1% predicted and lung density decline were correlated, but were artificially separated in the transition estimates; because of this, clinically implausible transitions were possible in the model.
- The analysis assumed the change in FEV1% predicted was independent of current FEV1% predicted level, which was clinically implausible.
- The treatment effect of human A1PI on FEV1% predicted was based on the wrong results from the updated Chapman et al. meta-analysis.
- Data from RAPID-OLE were included in the estimates of lung density decline transitions without adjustment for people switching treatment.

The committee acknowledged the ERG's concerns. In particular the committee was concerned that the evidence suggested FEV1% predicted and lung density decline were correlated, but these outcomes were implemented independently in the model and this would make the results uncertain. During consultation the company presented scenario analyses exploring the correlation between FEV1% predicted and lung density decline. The committee noted that this had a minimal effect on the cost-effectiveness results. It agreed that the meta-analysis results had been incorrectly applied in the company's analysis and accepted the ERG's amendment. During consultation the company correctly applied the meta-analysis results for patients with FEV1% predicted 30% to 50%. It noted

that most patients in the RAPID trial had FEV1% predicted less than 65% and therefore also applied these same values to the FEV1% predicted greater than 50% states. The ERG reviewed the meta-analysis, and presented results based only on observational studies; it applied the resulting treatment effect (which was statistically significant) to all patients with FEV1% predicted greater than 30%. The committee recalled that it had not been possible to measure the long-term effects of treatment on lung function in clinical trials because of the small number of patients and the likely time needed to detect a treatment effect. It therefore agreed that, although randomised controlled trials are normally the most methodologically robust studies, the follow-up time in the clinical trials may have been insufficient to assess decline in FEV1. The committee therefore concluded that the revised meta-analysis results using only observational evidence should be used to model treatment effect.

Survival

4.20 To model survival, the company used data from RAPID in the early stages of the model and data from a survival analysis of 110 patients from ADAPT (Green et al.) to model later survival with separate curves for the different FEV1% predicted and lung density decline states. During consultation the company also included the effect of A1PI on survival by applying the hazard ratio from the AlphaNet-ADAPT analysis (see section 4.15) to the survival data from Green et al. The ERG highlighted concerns with the modelling of survival across FEV1% predicted and lung density decline states, commenting that the link between these states and mortality is not well established and so the results should be interpreted with caution. The ERG also highlighted concerns with using data from RAPID; there were very few deaths in RAPID and the company incorporated RAPID-OLE data in the analysis without adjusting for people who switched treatment. The ERG noted that when switching from the RAPID and RAPID-OLE survival curves to ADAPT the company allocated people on human A1P1 and people on placebo to different points on the ADAPT survival curve. The ERG explained that this would underestimate

survival in the best supportive care group and overestimate it in the human A1PI group. The consequence of this was that, in the model, human A1PI had an additional survival benefit on top of the survival benefit associated with slowing lung function and lung density decline. The ERG clarified that the hazard ratio used by the company came from an analysis that included people without symptomatic lung disease. It also noted that applying the hazard ratio to the Green et al. data is not methodologically robust, because of the baseline imbalances between the 2 data sets.

4.21 The ERG explained that because of its concerns with the RAPID data and the company's modelling approach, it preferred to only use data from patients with lung disease in both the AlphaNet-ADAPT cohorts to model survival. The ERG estimated survival by treatment arm, meaning that the company's approach of using slower transition to states of poor lung function to capture any drug effect on survival was not included in the ERG's model. In considering these results the committee recalled the limitations of the ADAPT data set. The committee was concerned that absolute survival may have been overestimated because ADAPT may include people with a lower burden of disease than expected in the A1PI deficient UK population (see section 4.9). This would increase the total costs of both A1PI treatment and best supportive care. Conversely, it noted that the relative survival gain may have been underestimated if matching did not fully correct for differences between ADAPT and AlphaNet. This would underestimate the benefits of A1PI treatment.

4.22 The committee acknowledged that there were methodological issues with the company's approach. It considered that the ERG's approach to modelling survival was methodologically more appropriate, although it too had potentially important limitations. The committee concluded that given the evidence presented, the ERG's approach was more appropriate to use in its decision-making, but agreed that estimates of mortality remain a critical uncertainty in the model.

Lung transplant

4.23 The committee was aware that a key proposed benefit of treatment is the potential to delay or avoid lung transplant. However, the ERG explained that delaying lung transplant was associated with worse cost-effectiveness outcomes in the company's original model, but with better cost-effectiveness outcomes in the revised modelling. The committee understood that this difference was strongly driven by the assumptions and outcomes associated with lung transplant in the model. Therefore it was critically important to consider the plausibility of the modelling of lung transplant in detail.

4.24 The company's original model assumed that everyone with FEV1% predicted less than 30% would be eligible for lung transplant, regardless of the rate of lung density decline or other characteristics. The clinical experts stated that they try to arrange for people to have a lung transplant at a time when their life expectancy is similar or worse than would be expected after a transplant (bearing in mind the 2-year waiting list for a lung transplant). In clinical practice, this would also take into account a score of 8 points or more on the BODE index (which includes BMI, airflow obstruction, dyspnoea, and exercise tolerance; for airflow obstruction, FEV1% predicted below 35% gives the highest score), comorbidities (the clinical experts stated that 30% to 50% may not be accepted for this reason), organ availability and patient choice (see section 4.2). The committee agreed that although the model was consistent with a level of FEV1% predicted that would increase the chance of having a lung transplant, it does not precisely match the eligibility criteria for lung transplant in practice. The ERG explored the effect of reducing the proportion of people eligible for transplant by 30% in a scenario analysis, and the company included this assumption in its post-consultation modelling. The committee agreed that reducing the proportion of people eligible for transplant by 30% may still overestimate the number of people with A1PI deficiency who have transplants in clinical practice. It was aware that the ERG explored an age cap for lung transplant in its

analysis. It noted that age was not an eligibility criterion in practice so it would be inappropriate to assume a specific age cut-off. The committee agreed that the assumptions around lung transplant eligibility remained uncertain, and the model may have overestimated the proportion of people having a lung transplant.

4.25 The company estimated mortality after lung transplant using data from the NHS blood and transplant report (2017), which reported 1-year and 5-year survival figures of 82% and 59% respectively. It stated that although not specific to people with A1PI deficiency, these figures would be expected to be reasonable estimates for this population. During consultation the company supported these figures with evidence from Fisher et al. and Stone et al. The ERG explained that the company simplified the survival after transplant modelling by estimating survival probabilities for specific years instead of applying a survival curve. The ERG corrected the company's manipulation of the post-transplant survival data and explored alternative survival estimates of 1-year and 5-year survival after transplant of 70% and 50% respectively, which the committee considered acceptable for decision making. The committee concluded that survival after transplant is highly uncertain, but is crucial for accurately modelling the effects of lung transplant within the treatment pathway.

4.26 The committee was aware that in the ERG's revised survival analysis scenario, lung transplants were excluded from the model. The ERG explained that this was because the AlphaNet-ADAPT data were censored for lung transplants, and when transplants were included in the model there was a higher rate of death after transplant than in the pre-transplant health state. The committee agreed that this was counterintuitive, and showed serious uncertainty in the modelling of survival and lung transplant. The ERG noted that, when lung transplants are removed from the modelling, much of the benefit of A1PI treatment can still be captured through the survival benefit and slowed decline in lung function and density. The committee noted that in clinical practice lung transplants are an integral part of the treatment pathway for a small

proportion of the population. Moreover, it recognised that the potential to delay or avoid lung transplant was thought to be a key benefit of A1PI treatment. It considered that, in principle, lung transplant should be included in the modelling of this condition. However, it noted the crucial uncertainties in the proportion of patients who would have transplants and the survival after transplant in the current modelling. The committee concluded that lung transplant had not been suitably modelled to appropriately capture both costs and health effects. On balance, it concluded that the ERG's analysis removing lung transplants from the economic model was preferred for decision making, but noted its important limitation. The committee was aware that lung transplant could have a substantial effect on the cost-effectiveness results, but could not predict either the direction of this effect or its size. It also concluded that a model which would allow the committee to consider the impact of lung transplant on the benefit of A1PI treatment with greater certainty, and which more closely reflected clinical practice, would be preferred.

4.27 The company estimated the effects of lung transplant on quality of life using utility values from people who have had a lung transplant. These were based on a weighted average of single and double lung transplant utility values from patients at 4 UK lung transplant centres. The committee noted that the company, ERG and clinical experts did not raise concerns about the validity or plausibility of the estimates. The committee took this to mean that any reduction in quality of life because of transplant complications were captured in these utility values. However, it considered that the fear expressed by patient experts (which it understood was substantial and caused much anxiety; see section 4.2) was not captured. The committee agreed that it would be reasonable to include pre-transplant anxiety in the model, noting that this could be done using utility estimates for people who had been on the transplant waiting list. During consultation, the company amended its economic model to reflect the committee's preference for including pre-transplant anxiety. The company weighted the utility of patients with an FEV1% predicted less

than 30% who would be eligible for a lung transplant. The committee concluded that the adjustment for pre-lung transplant utilities was no longer applicable when lung transplants are removed. But if lung transplants were appropriately modelled, this scenario would be acceptable for decision making and appropriately capture the health effects of transplant.

Utility values

4.28 The committee understood that the utility values in the economic model were linked to FEV1% predicted categories, but not to lung density decline. The patient and clinical experts explained that FEV1% predicted can vary substantially without people noticing a change in their health. The committee recognised that the link between FEV1% predicted and quality of life was not clear. The company explained that utility values in the model may have been underestimated because the effect of reducing lung density decline on quality of life was not captured. The ERG noted that there was evidence available to model differences in quality of life according to baseline lung density and lung density decline. During consultation the company provided additional scenario analyses in which the effect of varying utility values according to lung density was explored. The committee accepted that the company's amendment had only a small effect on the cost-effectiveness estimates. The committee also recalled that A1PI treatment could have immediate effects on quality of life, including a positive change in behaviour, although these were unproven (see section 4.3 and section 4.12). It recognised that this benefit was potentially substantial but was not captured in the utility values used in the model and would therefore have to be considered qualitatively.

4.29 The committee considered whether there may be alternative sources of evidence to inform the utility values in the economic model. Alternative sources of data that needed mapping to EQ-5D may have limitations, but it agreed that it could consider these given its concerns with the modelling of quality of life. The committee noted that some information had been submitted by stakeholders during consultation, including interviews with

patients who had had A1PI treatment (see section 4.12). The committee recognised that the treatment benefits in the model did not appear to fully capture the effects described in the patient testimonies. The committee concluded that further narrative evidence could allow it to consider with greater certainty the modelled benefits of A1PI treatment, if it were collected systematically.

4.30 The committee considered whether it was appropriate to capture the health effects of A1PI deficiency on carers and family members. It recalled comments from the patient experts that highlighted the physical and emotional effects of A1PI deficiency on carers and family members (see section 4.1). The ERG noted that it had concerns about the implementation of carer disutility in the company's economic model. The committee concluded that the health effects of A1PI deficiency on carers and family members were important to consider, but agreed it would do this qualitatively because it had concerns with the implementation of carer disutility in the model.

Costs

4.31 The committee considered the company's assumptions about the costs in the economic model. The company assumed that most people (75%) having human A1PI would be able to have it at home or in the community. The ERG highlighted that community nurse availability was limited, so administering human A1PI in the community could be challenging. It explored the effect of assuming 100% of treatment was administered in clinic in a scenario analysis. The clinical experts explained that administering human A1PI in the community would be feasible, and they expected that most people would have treatment in this setting. The committee accepted the clinical experts' comments, and agreed that the company's assumption of administration setting was reasonable.

4.32 The company explained that best supportive care costs would be the same in both treatment groups, so it was reasonable to exclude these costs from the model. The ERG noted that best supportive care costs

were unlikely to be the same because survival and lung transplant rates would not be equal across treatment groups. Both of these factors would affect cumulative best supportive care costs. The committee agreed that best supportive care costs would be unlikely to cancel out across treatment groups, but recognised that excluding these did not have much effect on the economic results.

4.33 The cost of CT densitometry was not included in the company's original base case. The company noted that CT densitometry was not needed to identify people eligible for human A1PI, or for the monitoring of disease progression. The committee recalled expert comments that CT densitometry was a valuable tool for assessing emphysema associated with A1PI deficiency (see section 4.4) and would increasingly be used in clinical practice. The committee recognised that CT densitometry may be used for assessing A1PI deficiency regardless of the availability of human A1PI. But because survival and lung transplant rates would not be equal across treatment groups, the costs of CT densitometry would differ between people having human A1PI and people having best supportive care. During consultation, the company updated its base case to include the cost of doing 1 CT scan per year but the costs of best supportive care remained unchanged. The committee acknowledged the ERG's concerns that the company had not included the costs of CT scans appropriately but instead amended the disease management costs. The committee concluded that the ERG's approach to modelling the additional costs was reasonable.

4.34 The committee discussed a scenario analysis presented by the company at consultation, which accounted for rebate payments made by the company under the statutory scheme for pharmaceutical pricing. The scenario analysis deducted rebate payments from the unit cost of A1PI treatment for the years 2019 to 2021. The company explained that rebate payment rates were fixed in the statutory scheme for the first 3 years (2019 to 2021) and that the payments could effectively be attributed to the acquisition cost of human A1PI. The committee noted that the company,

as members of the statutory scheme, could join the voluntary scheme for pharmaceutical pricing at short notice. So, there was no 'guarantee' that the rebates would be paid as modelled. The committee was also aware that rebate payments would be made to the Department of Health and Social Care, and not distributed to clinical commissioning groups or NHS England. It was unclear to the committee how rebates paid on the technology would be directly applied to the provision of NHS services, and so considered that the rebate payments may not affect the opportunity costs of acquiring the technology. The committee concluded that the statutory scheme payment mechanism was not relevant in considering the value for money of the technology in this evaluation, and therefore should not be included in its preferred analysis.

Discount rate

4.35 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) specify that the discount rate that should be used in the reference case is 3.5% for costs and health effects. However, they also state that a non-reference-case rate of 1.5% for costs and health effects may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to significant irrecoverable costs. The company, in its base case, incorporated a discount rate of 3.5% of costs and health effects but presented a scenario analysis at consultation which used a discount rate of 3.5% for costs and 1.5% for health effects. The committee considered that using different discount rates for costs and health effects did not reflect the methods guide, and that A1PI treatment did not fulfil the criteria for using the lower discount rate. It therefore concluded that changing from the reference case discount rate of 3.5% for costs and health effects was not justified.

Cost-effectiveness analysis results

4.36 The committee considered the results of the economic analysis, taking into account the company's updated base case, and the ERG's exploratory scenario analyses. It considered that the most plausible scenario was based on the following amendments to the company's updated base case:

- using the revised meta-analysis results which included only observational studies to calculate transition probabilities (see section 4.19)
- using AlphaNet-ADAPT data (including only people with symptomatic lung disease) to model mortality (see section 4.22)
- removing lung transplant from the model (see section 4.23)
- removing the treatment stopping rule for human A1PI (see section 4.18)
- including healthcare resource use costs of best supportive care and CT densitometry in both arms (see sections 4.32 and 4.334.31)
- discounting costs and quality-adjusted life years (QALYs) at 3.5% per year (see section 4.35).

Based on the committee's preferred assumptions the incremental cost-effectiveness ratio (ICER) was £648,948 per QALY gained. It was aware that this analysis omitted lung transplant, which was an important limitation, but the direction and size of the effect of this was unknown. The committee noted that some potential benefits were not captured in the cost-effectiveness analysis. It recalled that treatment with human A1PI may lead to a positive change in behaviour for people with A1PI deficiency, and agreed this would be of great importance to patients (see section 4.3). It agreed that because there was no robust quantitative estimate of carer disutility it would consider the benefit of treatment to families and carers qualitatively (see section **Error! Reference source not found.**). The committee considered the most plausible ICER (while aware that it did not include these uncaptured benefits), and separately

considered how those additional factors which were not or could not be quantified might impact on their interpretation of the ICER.

4.37 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement, as revealed by the number of additional QALYs gained. The committee noted that in all of the scenarios presented, including its preferred scenario, the incremental QALY gain associated with human A1PI was lower than 10 QALYs. The committee concluded that human A1PI does not meet the criteria for applying a QALY weight.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.38 The patient experts explained that A1PI deficiency affected their working choices, and therefore their economic situation. The committee acknowledged the patient experts' views on the importance of the financial effects. It heard that this was at least partly driven by the age at which the condition is often diagnosed, when many people have young families and important financial obligations. However, it was also aware that many technologies it has considered also have financial and social effects on young adults either as patients or carers. No evidence was presented to show that the effect of A1PI deficiency was more significant than other conditions. The committee recognised the economic and social impact of the condition on patients and families, but considered that it should not give additional weight to this aspect in its decision.

4.39 The NHS commissioning expert explained that there is currently no highly specialised service for delivering human A1PI. They noted that centres

could be identified without the need for a full service specification if human A1PI were recommended, but recognised the value of further collaboration within NHS services and careful service design. The patient experts were concerned that specific expertise in A1PI deficiency (as opposed to COPD in general) is needed for services delivering A1PI treatment to be effectively implemented in England. They explained that it would be especially important to consider patients who struggle with travel. A clinical expert suggested that A1PI deficiency services could be arranged using a shared care model and could take advantage of digital technologies. The committee was reassured that there were unlikely to be significant additional costs to consider for designing and delivering a service.

Managed access arrangement

4.40 The committee considered whether a managed access arrangement could be an option to address the uncertainties in the evaluation. It recalled that it could not recommend specific starting criteria for human A1PI, and that it may be possible to address this within a managed access arrangement. But it noted that some of the main uncertainties in the clinical and economic evidence, such as overall survival, survival after transplant and the economic model structure, might not be resolved within a managed access arrangement or could be addressed without it. The committee also noted that the most plausible ICER was substantially higher than can be considered value for money for a highly specialised technology. It considered that it had not seen evidence that human A1PI had plausible potential to be considered value for money. The committee was not convinced that a managed access arrangement would be appropriate at this stage.

Other factors

4.41 The committee considered the number of people who might have treatment with human A1PI. It recognised that the estimates were uncertain, but comparatively large in the context of a highly specialised

technologies evaluation. The population would be expected to grow if a disease-modifying technology were made available or if there was an increase in screening. It recalled that defining specific starting criteria might reduce the eligible population, but it was not able to recommend specific starting criteria (see section 4.4). The committee was aware that the comparatively large population increased the risks to the NHS associated with the costs of the technology and the uncertainties in the evidence.

4.42 The committee considered if there were any equalities issues for human A1PI. It acknowledged that human A1PI is a blood product and therefore may not always be appropriate due to religious reasons. It also noted comments that A1PI deficiency was a condition almost always found in people of European family origin. The committee agreed that these considerations could not be addressed within a highly specialised technologies evaluation and noted that its recommendation applied equally across religions and family origins. The committee considered whether there were any other aspects of the condition, treatment or population that needed an adjustment to its approach on the grounds of equalities, taking into account the severe and disabling nature of the condition. It considered that there were none and agreed that no adjustments were needed.

4.43 The committee discussed whether Respreeza was an innovative treatment for people with A1PI deficiency. It recognised that human A1PI was the first disease-modifying treatment available for A1PI deficiency to be licensed in the UK, but noted that Respreeza was not the only brand of A1PI worldwide. The committee noted that although Respreeza provided more benefit than current treatments, its benefit was not unique. Because of this, it concluded that there were no additional health-related benefits associated with innovation that had not been captured in the analysis.

Conclusion

4.44 The committee acknowledged that A1PI deficiency is a rare condition that has a substantial effect on patients and families. It understood that there was an unmet need for an effective treatment that protects people from the effects of infection and exposure to environmental toxins. It noted that people with A1PI deficiency altered their behaviour because of their vulnerability to lung tissue damage, with people often avoiding social interaction to reduce infection risk. It noted that the population eligible for treatment was uncertain and could be affected by introducing screening and defining treatment starting criteria. The committee considered that the available evidence showed that human A1PI reduced the rate of lung density decline more than placebo. It noted that it was plausible that A1PI treatment could provide benefits in quality of life, walking distance and lung function, although this was unproven. The committee concluded that A1PI improves survival, but there was substantial uncertainty in the available evidence and the size of this benefit was unknown. Overall, the committee considered that, human A1PI could provide meaningful clinical benefits. Taking into account the most plausible assumptions in the economic model, the committee was aware that the most plausible ICER was substantially above that normally considered value for money for highly specialised technologies, and that human A1PI did not meet the criteria for an additional QALY weight. The committee was also aware that some benefits associated with human A1PI had not been captured appropriately in the modelling, including quality-of-life benefits for both patients and carers, survival benefits in the UK population and benefits of lung transplant. It noted that including uncaptured benefits for patients and carers would improve the value for money of A1PI treatment, but the nature and size of the effects of survival and lung transplant were unknown. Bearing in mind that the preferred ICER was substantially above that normally considered value for money for highly specialised technologies and the additional risks posed by the large and potentially increasing population, it was not plausible that the uncaptured benefits would mean that A1PI treatment could be considered value for money.

Therefore, even considering the benefits not captured by the model, the committee concluded that A1PI treatment would not provide value for money in the context of a highly specialised service. Taking into account all of the available evidence, the committee did not recommend human A1PI as an option for treating emphysema in people with A1PI deficiency.

5 Proposed date for review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
November 2019

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Thomas Paling and Lorna Dunning
Technical leads

Ian Watson
Technical adviser

Joanne Ekeledo
Project manager

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