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 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 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: September 2018

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 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: 17 October 2018

Second evaluation committee meeting: 24 October 2018

Details of membership of the evaluation committee are given in section 6.

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

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 include therapies used to manage chronic obstructive pulmonary disease, which treat the symptoms but not the cause of the condition.

Clinical trial evidence suggests that human A1PI slows decline in lung density more than placebo. But there is no evidence of its benefit on lung function, quality of life or walking distance. There are some uncertainties, but evidence from the clinical trials and clinical experts suggests that human A1PI is likely to provide important benefits for people with A1PI deficiency.

The cost-effectiveness estimates for human A1PI are much higher than what NICE normally considers acceptable for highly specialised technologies. Therefore, it 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 alpha1-proteinase inhibitor (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 the summary of product characteristics for Respreeza 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; company submission).

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 AATD

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. Basic activities such as walking, speaking, dressing and eating become increasingly challenging as the disease progresses. Careful planning is needed to complete daily tasks when people are limited by breathlessness. The patient experts highlighted that 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. The committee acknowledged that A1PI deficiency severely affects people's ability to complete normal tasks, and understood that people may significantly change or limit their behaviour to reduce the risk of lung damage. The patient experts noted that A1PI deficiency affects emotional wellbeing as well as physical health. They explained that being physically and socially limited by A1PI deficiency can cause severe depression. Uncertainty about future health also causes substantial anxiety. They also highlighted that as A1PI deficiency progresses there is loss of independence and increasing reliance on help from family members and carers. This affects carers of people with A1PI deficiency emotionally, physically and financially. The committee 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 the period after transplant, and that the complications and ongoing health problems after surgery can be severe. The patient experts commented that lung transplant was a frightening prospect. The committee recognised that the risks associated with lung transplant make the decision to have the surgery challenging. 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 perceived as an important benefit for people with AATD. 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 CT lung densitometry was the most appropriate method to assess the progression of emphysema, because spirometry measures (such as FEV1) were not as reliable. They also explained that rate of decline in lung density (as measured by CT densitometry) could potentially be used to decide when to start treatment, but acknowledged that further work would be needed to define a specific rate of decline as a starting criterion. The committee recognised that defining specific starting criteria would affect the population size. The committee concluded that the most appropriate starting criteria for human A1PI have not been defined, and agreed that clearly defined starting criteria would help ensure that those most in need of treatment would have it.

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 company submitted evidence from 2 controlled clinical studies:

- The RAPID study was a randomised, double-blind, placebo-controlled trial, including 180 adults aged 18 to 64, comparing the efficacy and safety of human A1PI with placebo.
- RAPID-OLE was an open label extension of RAPID, including 140 people from RAPID, comparing 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).

The company also submitted clinical effectiveness evidence from systematic literature reviews, meta-analyses and a US registry. 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 FEV1% predicted categories. Survival data from the US registry, the Alpha-1-Antitrypsin Deficiency Registry Study Group (1998), were also considered.

4.7 The ERG explained that 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.

Clinical trial results

4.8 The committee discussed the lung density results:

- RAPID: at 24 months there was a greater reduction in lung density decline at total lung capacity in people who had human A1PI (−1.45 grams/litre/year) than in 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 A1P1 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 clinical benefit.

4.9 The committee noted that for secondary outcomes (including lung function, quality of life and walking distance) there was no statistically significant benefit from human A1PI treatment. It noted that there was a

greater decline in lung function (FEV1% and diffusing capacity of the lungs for carbon monoxide [D_{LCO}]) for people who had human A1PI than for those who had placebo. However, the clinical experts explained that the size of the difference in effect would not be considered clinically significant, and the committee recognised that the difference was not statistically significant. The committee noted that the results from the updated Chapman et al. meta-analysis showed that human A1PI reduced lung function decline compared with no treatment in people with FEV1% predicted less than 65%. However, in people with FEV1% predicted over 65% there appeared to be a greater benefit for people who did not have treatment. The committee also considered data on quality of life (St George's Respiratory Questionnaire) and walking distance (incremental shuttle walk test) from the RAPID studies. 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. It also noted that there was a greater improvement in walking distance for people on placebo. However, it recognised that the differences in quality of life and walking distance were not statistically significant. The committee concluded that the results from the secondary outcomes of lung function, quality of life and walking distance were inconclusive but there was no evidence that human A1PI provided benefits for these outcomes.

4.10 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 was not what would be expected. The clinical experts acknowledged that this was a potential cause for concern, although they highlighted that definitions of pulmonary exacerbations vary and can be subjective. The committee also considered differences in the rate of pulmonary exacerbations between groups in RAPID; however, the results are academic in confidence and cannot be reported here. The committee

expressed concern that human A1PI may be associated with an increased risk of pulmonary exacerbations.

4.11 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 who had previously had, human A1PI had a higher probability of survival than those who had not. The committee recognised the limitations of this observational evidence, but concluded that this suggested that human A1PI may improve survival.

Cost to the NHS and value for money

Economic model

4.12 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 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. 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, and it was not fully convinced that the current model structure precisely reflected the progression of the disease. However, it concluded that, taking into account the available evidence to link FEV1% predicted and lung density to health and economic outcomes, the company's rationale was logical and the model could be considered for decision-making.

4.13 The committee considered the thresholds of lung density decline applied 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 model structure.

4.14 The committee considered the population included in the company's economic model. The model assumed that everyone starts in any of the lung density decline states in the FEV1% predicted 30% to 50%, or over 50% groups. The ERG noted that 1 of the company's proposed criteria for starting treatment with human A1PI was either rapid lung function decline or rapid lung density decline. It highlighted that this starting criterion was not implemented in the economic model. The committee recalled that

starting criteria for human A1PI had not yet been defined (see section 4.4). The ERG removed a stopping rule from the economic model that stopped human 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 the starting criteria in the model should be in line with clinical practice, and accepted that the model population was appropriate. It further concluded that if starting or stopping criteria (or both) for human A1PI were defined, it would be appropriate to implement these in the economic model.

Transition probabilities

4.15 To model transitions between the health states, the company used data from RAPID, a UK database (ADAPT), and the updated Chapman et al. meta-analysis (see section 4.6). Transition probabilities between the FEV1% predicted categories and the lung density decline categories were derived separately. 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% and lung density decline were correlated, but these outcomes were implemented

independently in the model and this would make the results uncertain. It agreed that the meta-analysis results had been incorrectly applied in the company's analysis and accepted the ERG's amendment. The committee concluded that a model accounting for the correlation between FEV1% predicted and lung density could reduce uncertainty.

Survival

4.16 To model survival, the company used data from RAPID in the early stages of the model and data from a UK database (ADAPT) to model later survival. The company applied survival curves to each of the FEV1% predicted and lung density decline states. 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. So this meant that human A1PI was given an artificial additional survival benefit in addition to its effect on slowing lung density and lung function decline. The clinical experts explained that ADAPT had important limitations. The committee recognised this, but was aware that ADAPT was used in both the company's and ERG's scenarios so it was not presented with evidence to resolve these limitations. 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 ADAPT to model survival using slower transition to states of poor lung function to capture any drug effect on survival. The committee acknowledged that

there were methodological issues with the company's approach, and agreed that the benefits of human A1PI were already captured by it slowing transition to states of poor lung function. Therefore, it considered that the ERG's approach to modelling survival was methodologically more appropriate. The committee considered the plausibility of the estimates of overall survival gain with human A1PI produced by the company (3 years) and ERG (7 months). It recalled real-world survival data from the US registry (see section 4.11), and accepted that it was plausible that human A1PI could substantially increase survival. The committee recognised that a 7-month survival gain might be conservative, but was unable to establish whether a 3-year gain would be plausible. It considered that the US registry data could be used to inform the survival modelling, or, at a minimum, validate the modelled survival outcomes. The committee concluded that given the evidence presented, the ERG's approach was more appropriate to use in its decision-making, but agreed that mortality remains a critical uncertainty in the model.

Lung transplant

4.17 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 this was associated with worse cost-effectiveness outcomes in the company model. The committee acknowledged that this effect 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.

4.18 The company 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 committee recalled comments from the patient experts that the risks associated with lung transplant made it a frightening prospect (see section 4.2). The clinical experts stated that they attempt 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). The committee considered that it might be possible to more accurately reflect this principle in the model by restricting lung transplants to those in the last years of life. In clinical practice, lung transplant would be considered only for people with a score of 8 points or more on a composite measure known as the BODE index, which includes BMI, airflow obstruction, dyspnoea, and exercise tolerance. To have the highest score in the airflow obstruction criterion of the index, people must have FEV1% predicted below 35%. 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 committee discussed whether there would be anyone who would be considered for a lung transplant but not have one because of factors such as comorbidities or age. The clinical experts explained that people with A1PI deficiency are less frequently rejected for transplant because of comorbidities than people with other conditions, but that 30% to 50% may not be accepted. The ERG noted that it explored the effect of reducing the proportion of people eligible for transplant by 30% in a scenario analysis. The committee agreed that given the clinical experts' comments this was reasonable to include in the model. It was aware that the ERG explored an age cap for lung transplant in its analysis, but noted that age was not an eligibility criterion in practice. It gathered from the clinical experts that patients with A1PI deficiency were on average younger than other patients considered for lung transplant. Therefore, it agreed that it would be inappropriate to assume a specific age cut-off. The committee concluded that the ERG's scenario capturing a proportion of people ineligible for transplant was appropriate for decision-making, but agreed that the assumptions around lung transplant eligibility remained uncertain.

4.19 The company estimated mortality after lung transplant using data from the NHS blood and transplant report (2017). The company noted that 1-year and 5-year survival figures were 82% and 59% respectively, which,

although not specific to people with A1PI deficiency, would be expected to be reasonable estimates for this population. The ERG noted that the company simplified the survival after transplant modelling by estimating survival probabilities for year 1 and subsequent years instead of applying a survival curve. The ERG corrected the company's unnecessary manipulation of the survival data in estimating mortality probability after transplant. The committee accepted the ERG's amendment, and that modelling survival after transplant using a survival curve may have been preferable. The ERG explained that the reporting of survival after transplant is generally poor, and provided alternative estimates for survival after transplant from clinical experts and a UK transplant audit (2000). Based on this, the ERG estimated 1-year and 5-year survival after transplant at 70% and 50% respectively. The committee noted that survival after transplant was a key driver of the model, and acknowledged that both survival estimates were uncertain. But the clinical experts explained that the ERG's estimates were reasonable, and the committee considered that the ERG's estimates were plausible and could be used in its decision-making. The committee concluded that survival after transplant is uncertain, and agreed that further evidence would be welcome. Overall, the committee agreed that the ERG's figures were acceptable for decision-making.

4.20 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 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 due to the complications of transplant 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. The committee concluded that the health effects of lung transplant after transplant had been appropriately captured, but the additional health effects before the transplant were not.

Utility values

4.21 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, with people not having any noticeable 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. The committee agreed that, given its concerns about the link between FEV1% predicted and quality of life, it would have liked to consider an analysis in which utility values varied according to lung density. The committee also recalled its earlier conclusion that the protection given by human A1PI could lead to a positive change in behaviour (see section 4.3). It recognised that this benefit was potentially substantial but was not captured in the utility values used in the model. 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 concluded that it was not convinced that the approach to modelling quality of life appropriately reflected the course of the disease, and agreed it would have liked to consider the effect of lung density decline on utility values. It further concluded that the health benefit

of behaviour change had not been captured quantitatively and it would therefore be considered qualitatively.

4.22 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

4.23 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. 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 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. The cost of CT densitometry was not included in the company's economic model. 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. The committee concluded that it had concerns with the modelling of costs, and agreed that it would prefer best supportive care and CT densitometry costs to be included.

Cost-effectiveness analysis results

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

- using different results from the updated meta-analysis to calculate transition probabilities (see section 4.15)
- using the UK registry survival data to model mortality (see section 4.16)
- removing the treatment stopping rule for human A1PI (see section 4.14)
- reducing the population eligible for lung transplant by 30% (see section 4.18)
- using the ERG's alternative estimates of survival after transplant (see section 4.19).

Based on the committee's preferred assumptions the incremental cost-effectiveness ratio (ICER) was £8,069,855 per quality-adjusted life year (QALY) gained. The committee noted that the ICER was driven by low incremental QALY gains for human A1PI (0.048). It also 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). The committee also recalled that the fear and anxiety of people waiting for lung transplants was not captured. Given the patient experts' statements, it agreed that this was important to consider (see sections 4.2 and 4.20). 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 4.22). The committee considered the most plausible ICER in the context of these uncaptured benefits.

4.25 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 much 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

4.26 The committee understood that A1PI deficiency can cause people to retire early. The patient experts explained that A1PI deficiency affected their working choices, and therefore their economic situation. The committee acknowledged comments that the limitations caused by A1PI deficiency can affect people's relationships. It recognised that human A1PI could have an effect beyond health benefits, but it noted that the full effect of these benefits had not been quantified. It agreed to consider these benefits in its decision-making.

4.27 The NHS commissioning expert explained that there is currently no highly specialised service for delivering human A1PI. But centres could be identified without the need for a full service specification if human A1PI were recommended. The committee was reassured that there were unlikely to be significant additional costs for designing and delivering a service to take into account.

Managed access arrangement

4.28 The committee considered whether a managed access arrangement could be an option to address the uncertainties in the evaluation. It acknowledged that the starting criteria for human A1PI have not been fully defined, 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, but that improvements in the economic modelling would be valuable.

Other factors

4.29 The committee considered the size of the population who may be considered for treatment with human A1PI. It recognised that the estimates were uncertain, but were nevertheless comparatively large in the context of a highly specialised technology. It also heard that the population would be expected to grow if a disease-modifying technology were made available or if there was an increase in screening, or both. But it recalled that defining specific starting criteria might reduce the eligible population (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.

4.30 The committee considered if there were any equalities issues for human A1PI. The committee acknowledged that human A1PI is a blood product and recognised that because of this it may not be used by people of certain religions. 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.

4.31 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

4.32 The committee acknowledged that A1PI deficiency is a rare condition that has a substantial effect on patients and families. It was aware that emphysema resulting from A1PI deficiency causes severe symptoms, including breathlessness, which limit people in their usual activities and could lead to a loss of independence as the condition progresses. 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. However, it noted that the results of the secondary outcomes in the RAPID studies were inconclusive but that there was no evidence that human A1PI provides benefits in lung function, quality of life and walking distance. The committee considered that it expected there to be some survival benefit associated with human A1PI, but there was substantial uncertainty in the available evidence. Overall, the committee considered that, although the evidence was uncertain, 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, including a potential positive change in behaviour, delaying or avoiding the fear and anxiety of people waiting for transplant, and the reduction in the disutility experienced by carers of people with A1PI. 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, even considering the nature and potential size of benefits not captured by the model the committee did not alter its conclusion. The committee was concerned that the very low QALY gains were strongly influenced by the uncertain survival estimates, and might change substantially if there were better overall survival data that were modelled appropriately. However, based on the evidence available 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 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
September 2018

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
Technical Lead

Ian Watson
Technical Adviser

Joanne Ekeledo
Project Manager

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