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Clinician and Patient Involvement Group (CAPIG)
Summary of meeting held on 2nd December 2016
Human alpha1-proteinase inhibitor (Respreeza®▼) 1,000 mg powder and solvent for solution for infusion

Marketing authorisation holder

CSL Behring UK Ltd

Licensed indication

Human alpha1-proteinase inhibitor (Respreeza®) for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (e.g. 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 (e.g. lower forced expiratory volume per second [FEV_1] predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency.

Company's proposed positioning (if any)

Within the licensed indication, the company also propose that patients should meet all of the following criteria before being considered for treatment with Respreeza®:

- A diagnosis of severe alpha1-proteinase inhibitor deficiency (<11 µM)
- PiZZ, PiZ (null) or Pi (null,null) genotypes
- Forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) < 0.7 (indicating moderate airways obstruction) or emphysema demonstrated by computed tomography (CT) scan via multi-disciplinary team consensus
- FEV_1 30 – 70% predicted
- Rapidly declining lung function (as measured by FEV_1 or diffusing capacity of carbon monoxide [DLco]) or lung density decline (measured by emphysema on CT scan)

1. Severity of the condition

Alpha1-proteinase inhibitor (A1-PI) deficiency is a rare genetic disorder in which patients who are severely A1-PI deficient are susceptible to inappropriate proteolysis of lung tissue, leading to emphysema. Symptoms become apparent in the third to fourth decade of life with a usual progression to severe respiratory insufficiency and premature death. Accurate diagnosis is typically delayed by 6-8 years due to a general lack of awareness and understanding of A1-PI deficiency. Patients may appear to look healthy, which can mask the seriousness of the condition, and have generally lost a significant proportion of lung function before A1-PI deficiency is identified. A1-PI deficiency-related emphysema and symptoms are progressive and can progress rapidly even in patients who have never smoked.

Emphysema in patients with severe A1-PI deficiency causes considerable morbidity and early mortality and represents a major burden for patients in addition to a profoundly deleterious effect on patients' and carers' quality of life. Breathlessness is the key symptom and results in disastrous effects of the disease in all areas of life.

Simple tasks such as showering, housework and even talking become difficult and significant planning is required for routine events such as shopping. As a result of their symptoms and a fear of infection, patients find it increasingly difficult to participate in family life and social occasions leading to social isolation, which can severely impact their mental health. Loss of independence and the accompanying loss of income, often when young, places increasing strains on patients and their families and further impacts patients' mental health.

Frequent infective exacerbations, often requiring hospital admission, lead to a faster decline in breathlessness which further compounds the negative effects on patients' mobility, ability to self-care and to participate in family and social life. At the severe stage of the disease most patients are house- or even bed-bound, having to rely on carers around the clock. Patients become dependent on supplementary oxygen and largely lose the ability to self-care.

2. Unmet need

Current treatment options for A1-PI deficiency-related emphysema reduce symptoms only. Symptomatic treatments include inhaled bronchodilators and inhaled steroids, mucolytic therapy, antibiotics and systemic corticosteroids during exacerbations, and oxygen therapy (as required or long-term). Access to pulmonary rehabilitation is limited within Wales. Current treatments do not address the underlying A1-PI deficiency or the progressive loss of lung tissue and, therefore, do not stabilise the patient's physical decline, improve any of the adverse consequences of A1-PI deficiency or improve their quality of life. Patients need treatments that decelerate, halt or reverse disease progression to prevent severe breathlessness, frequent respiratory infections and hospital admissions. A1-PI augmentation therapy has been used for almost two decades in the U.S., Canada and some European countries. Human alpha1-proteinase inhibitor (Respreeza®) is the first augmentation product licensed in the UK for the treatment of emphysema due to A1-PI deficiency.

In their written submission the patient organisation suggested that human alpha1-proteinase inhibitor could bridge the gap to lung transplantation. However, they also added that many patients choose not to undergo transplantation because the risk of complications is high, the median survival rate after transplantation is low, side effects and complications of the anti-rejection medication can be significant and the need for intensive monitoring can be prohibitive. The availability of donor organs is also very limited. Some patients decline the offer of transplantation as they feel unable to cope with the psychological impact of such a major and risky intervention. Clinicians expressed the view that lung transplantation was a last resort.

3. Added value of the medicine for the patient:
3a. How would this medicine be expected to add value to the patient's wellbeing and experience of care?

Access to augmentation therapy would be a step changing improvement for the management of A1-PI deficiency-related emphysema. In European countries and the U.S. where augmentation therapy has been available for many years patients have reported their breathlessness progressing more slowly, stabilising or even improving after initiation of treatment with human alpha1-proteinase inhibitor. Patients and experts in European countries and the U.S. have also reported a reduction in the frequency and severity of acute pulmonary infections. Milder infections allow patients to manage these acute episodes themselves or with their GP rather than having to see a specialist or go to hospital for emergency admissions. In a survey conducted by the Alpha-1 UK Support Group, 39% of patient respondents said that in the preceding five years they had attended Accident and Emergency due to severe exacerbations and one third were admitted to hospital (often multiple times) for their condition. Hospital admissions have a significant impact on a patient's independence and quality of life

and incur expenses for the patient. Following severe lung infections, patients often experience a faster decline in their breathlessness and there is an increased risk of mortality associated with exacerbations. Therefore, reducing the frequency and severity of exacerbations is an important treatment goal which will have the benefit of improving patients' quality of life, and help to preserve their independence, mobility and employment for longer. It will also reduce the use of antibiotics and steroids which has benefits for patients (reduced risk of adverse effects associated with these medicines) and reduces the use of NHS resources.

During the meeting the patient organisation made reference to a small number of case reports from patients receiving human alpha1-proteinase inhibitor in which significant benefits in activity levels, quality of life, ability to stay in employment for longer, and participation fully in family, social and community life were reported. The company also made reference to a small survey conducted by the Alpha One Foundation in patients who continued to receive Respreeza® on a compassionate use basis after completion of the pivotal RAPID study (approximately 20 patients). Stabilisation of the condition, reduction in frequency and severity of exacerbations, improved ability to work, be active and lead a fulfilled family and social life were reported by patients in this survey.

Treatment with human alpha1-proteinase inhibitor is estimated to extend survival by three years in the company model, though this figure is considered to be an underestimate by one clinical expert at the meeting. An extension in survival would mean that patients could continue to be active at home and in the workplace and be less reliant on third-party care (family members, NHS and social care staff) for longer. Patients are typically diagnosed with A1-PI deficiency in their 40s, which is generally the peak of a person's career and therefore the age associated with highest pay and the greatest tax contributions to society. By initiating patients on treatment with human alpha1-proteinase inhibitor early from diagnosis patients would have the greatest chance of staying in work, being financially better off, contributing to society and leading normal lives. Initiating treatment with human alpha1-proteinase inhibitor would also give patients the added benefit of regular contact with a healthcare professional, enabling closer monitoring, access to clinical advice and early identification (and management) of disease-related complications.

The emotional impact of gradually losing independence is of much concern to patients. Reduction of the mental distress that is associated with the progressive loss of independence, particularly loss of the ability to self-care and the isolation felt by patients who are no longer able to actively participate in life, would be an immense benefit for patients. There would also be a positive emotional impact for patients knowing they are receiving a medicine that treats the underlying deficiency.

3b. How is this medicine better than current treatments?

Emphysema due to severe A1-PI deficiency causes irreversible lung damage and significantly reduces patient life expectancy, with estimates of yearly mortality of 7.5% in patients treated with best standard care. Current standard care involves only symptomatic treatment and does not address the underlying disease. Human alpha1-proteinase inhibitor slows the progression of emphysema in adults with severe A1-PI deficiency. Mean decline in lung density during the two year pivotal study was reduced by 34% compared to placebo. One clinical expert also reported during the meeting that there are published data on the reduction of exacerbation severity with augmentation therapy, which is also reported by users of augmentation therapy in the U.S. and European countries. Human alpha1-proteinase inhibitor has a good safety profile and has shown no risk of viral transmission.

3c. Does this medicine have the potential to make a significant and substantial impact on health related benefits?

By slowing or halting the rate of lung density decline and, as suggested in the company model, extending life by three years patients will remain in employment for longer or be able to return to work. Based on patient reports from other countries where human alpha1-proteinase inhibitor is available, health related benefits are expected to include a reduction in the frequency and severity of pulmonary infections, exacerbations, and scheduled and unscheduled hospital admissions, with the consequent benefits to patients in terms of their independence and quality of life. It would also provide hope to patients who currently face a future where there is nothing that can slow down the progression of their disease.

4. Added value of the medicine for the patient's family or carers

As disease progression occurs patients rely more and more on family and carers for assistance in performing simple everyday tasks, with medical appointments and during hospital admissions. This places an increasing time commitment and financial burden on family and carers to such an extent that they may have to reduce or give up employment. The carer may also be the sole provider if the patient has had to give up employment, which is very difficult in itself, but even more difficult when coupled with increased care duties for the patient and providing for the needs of other family members. Carers of patients feel that their own health suffers as a result of the increased demands placed on them. Children may also, from an early age, have to provide assistance and care for parents with A1-PI deficiency-related emphysema, which patients feel deprives them of a normal childhood. By enabling patients to remain in employment and retain their independence for longer, human alpha1-proteinase inhibitor would reduce the financial and emotional burden on patients' families and carers and offer them invaluable time.

5. What is the most appropriate position for the medicine in the pathway of care for the condition? Does this differ from the company's proposed positioning?

The company positioning does not describe prior treatments or non-pharmacological interventions, only stating that they should be optimised. Clinicians advise that a pulmonary rehabilitation programme should have been completed and patients should be required to have demonstrated smoking cessation for a period of time. Patients should initially be assessed in specialist units with ongoing monitoring to identify those patients who would benefit most.

6. Are there specific patient groups for whom the medicine is particularly beneficial? If so, please specify

Patients whose health is rapidly declining as a result of A1-PI deficiency-related emphysema and those with frequent exacerbations would particularly benefit from treatment with human alpha1-proteinase inhibitor.

7. Are there any important considerations in relation to treatment delivery (e.g. how treatment should be monitored, how long it should be continued etc.)?

Respreeza® is administered as an intravenous infusion once weekly. It has a potential for hypersensitivity reactions, but the risk is low. Initial treatment should be given in specialist units and patients should be carefully monitored.

8. Other considerations

There are no A1-PI deficiency specialist centres in Wales. It was suggested that

treatment would be better provided through such specialist centres, with development of commissioning arrangements regardless of appraisal outcome. The option of establishing satellite A1-PI deficiency clinics in Wales, with specialists visiting from existing centres, was also discussed. This would reduce patient travel and provide specialist training to physicians in Wales, with the aim of eventually having specialist A1-PI deficiency centres in Wales that are led by local physicians who have built expertise over time in the satellite clinics.

9. Is there a key factor, or combination of factors, that would justify this medicine being available in NHS Wales?

- Human alpha1-proteinase inhibitor (Respreeza®) is the first and only treatment for A1-PI deficiency-related emphysema licensed in the UK.
- Human alpha1-proteinase inhibitor is the only treatment that targets the underlying cause of A1-PI deficiency-related emphysema; currently available medicines reduce the symptoms of the condition.
- Human alpha1-proteinase inhibitor has been shown to slow the progression of emphysema in adults with severe A1-PI deficiency and, according to expert input at the meeting, reduce exacerbation severity.
- There is a disparity in availability of augmentation therapy between patients with A1-PI deficiency-related emphysema in Wales and those in other European countries, Canada and the U.S. Human alpha1-proteinase inhibitor is expected to help patients retain their personal and financial independence for longer, improving the quality of life for themselves and their family and/or carers.
- UK patients state that knowing they are receiving a medicine that treats the underlying deficiency would have a positive emotional impact and provide them with hope.

It should be noted that one expert involved in compiling this response declared a personal specific interest in relation to human alpha1-proteinase inhibitor for the indication under consideration. The patient organisation involved in compiling this response has received unrestricted educational funding from CSL Behring UK Ltd.