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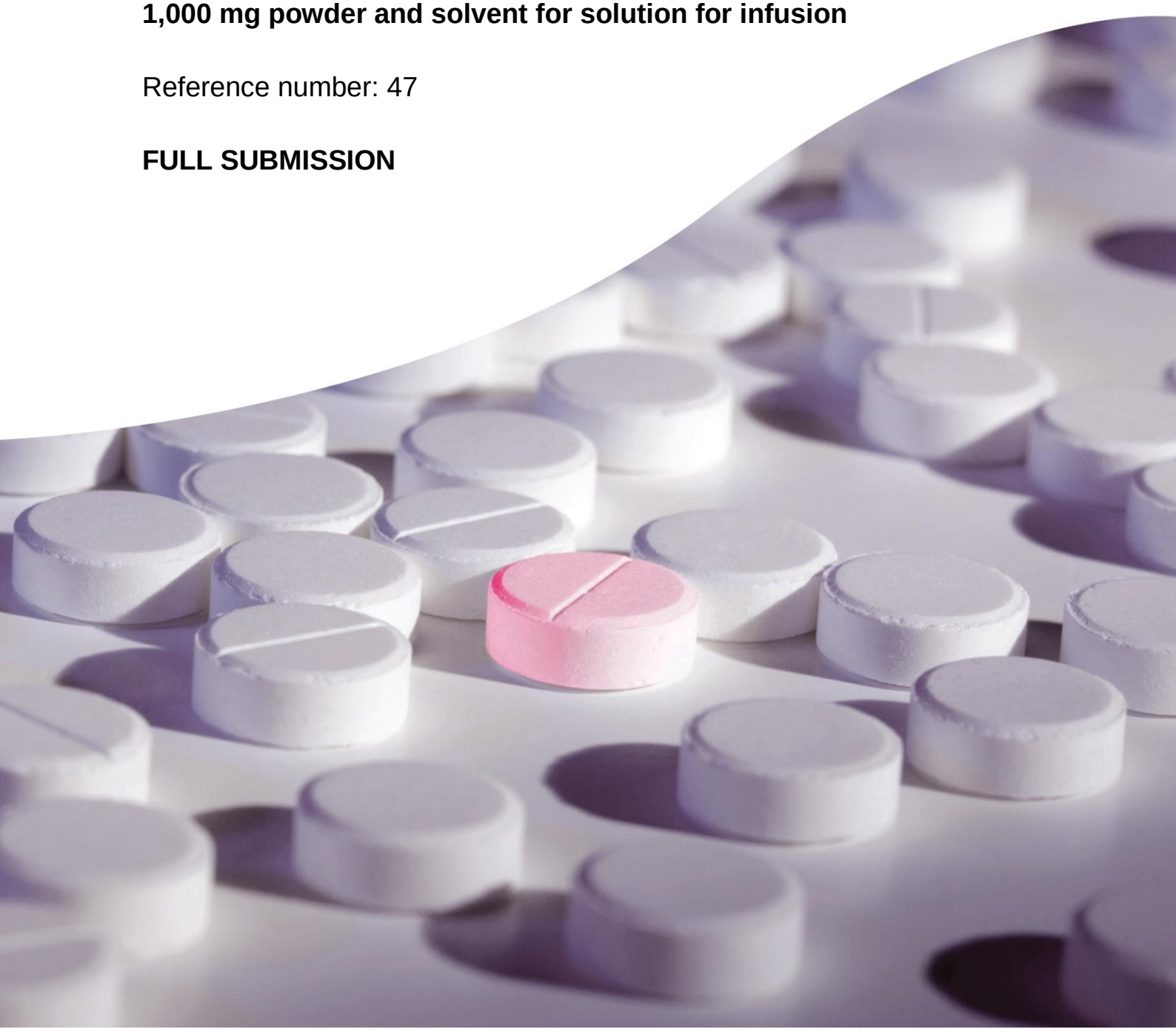
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Human alpha1-proteinase inhibitor (Respreeza®▼)
1,000 mg powder and solvent for solution for infusion

Reference number: 47

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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AWMSG Secretariat Assessment Report
Human alpha1-proteinase inhibitor (Respreeza®▼) 1,000 mg powder and solvent for solution for infusion

This assessment report is based on evidence submitted by CSL Behring UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	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[2].
Dosing	The recommended dose is 60 mg/kg body weight administered by intravenous infusion once weekly. First infusions should be administered under the supervision of a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency. Subsequent infusions can be administered by a caregiver or by the patient. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	20 August 2015[2]
UK launch date	September 2016[1]

2.0 DECISION CONTEXT

2.1 Background

Alpha1-proteinase inhibitor (A1-PI) deficiency is a genetic disorder caused by mutations in the SERPINA1 gene[3]. The most common deficiency alleles in Northern Europe are PiZ and PiS. The PiZZ genotype is present in the majority of individuals with severe A1-PI deficiency and in the majority (> 95%) of all patients with severe emphysema caused by A1-PI deficiency[3].

Endogenous A1-PI inhibits the protease enzyme neutrophil elastase (NE). In the lungs NE causes proteolysis of lung tissue[3-5]. Patients who are severely A1-PI deficient are therefore susceptible to inappropriate proteolysis of lung tissue by NE, leading to emphysema[3]. Symptoms often become clinically apparent in the third to fourth decade of life with a usual progression to severe respiratory insufficiency and premature death[3].

Treatment options for emphysema associated with A1-PI deficiency in the UK follow chronic obstructive pulmonary disease (COPD) guidelines and include: inhaled bronchodilators, inhaled corticosteroids, oxygen therapy, mucolytics, antibiotics and systemic corticosteroids (during exacerbations), and pulmonary rehabilitation[6]. These aim to maintain respiratory health and delay the need for lung transplant surgery. However, they do not address the underlying cause of the A1-PI deficiency[6]. A1-PI augmentation offers a direct approach to therapy, re-establishing the protease/anti-protease balance in the lower respiratory tract[3,7].

Respreeza®▼ is an enzyme replacement (augmentation) therapy containing human A1-PI, isolated from human plasma, as the active substance[1,2]. In their submission the company suggest that treatment should be initiated only in patients who meet all of the following criteria:

- A diagnosis of severe A1-PI 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]

2.2 Comparators

The comparator included in the company submission was best supportive care[1].

2.3 Guidance and related advice

There are no UK specific guidelines for A1-PI deficiency with management following standard COPD therapy.

- NICE Clinical Guideline 101. Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2010)[8].
- American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency (2003)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from the pivotal randomised, double blind, placebo-controlled, multi-centre Phase III/IV RAPID study (CE1226_4001) and its corresponding two-year open-label extension study (CE1226_3001).

3.1 RAPID study (CE1226_4001)

A total of 180 patients aged 18 to 65 years with emphysema secondary to A1-PI deficiency (serum A1-PI levels < 11 µM) and an FEV_1 ≥ 35% and ≤ 70% predicted were randomised in a 1:1 ratio to receive weekly intravenous infusions of Respreeza®▼ 60 mg/kg body weight (n = 93) or placebo (n = 87) over a two year period[1,3,10]. The majority of subjects (93%) presented with the PiZZ genotype of A1-PI deficiency[1,10].

The primary efficacy endpoint was the annual rate of lung density decline measured by CT scan at total lung capacity (TLC: volume of gas present in the lungs after maximal inspiration), functional residual capacity (FRC: volume of gas present at end-expiration during tidal breathing) and TLC/FRC combined states[1,10]. Respreeza®▼ treatment resulted

in a significantly slower annual rate of lung density decline compared to placebo (−1.45 g/L versus −2.19 g/L) when measured at TLC only and a non-significant trend towards a slowing rate of lung density decline when measured by FRC only and TLC/FRC combined (Table 1)[1,10].

Key secondary endpoints of exercise capacity (assessed by the incremental shuttle walking test), change in symptoms (assessed by the St. George's Respiratory Questionnaire) and rate of pulmonary exacerbations showed no significant difference between treatment groups[1,3,10].

Table 1. Comparison of annual rate of decline in lung density* (g/L) in the RAPID Study[1,3,10]

Inspiration State	Treatment (n)	Point estimate (SE)	Difference Respreeza®▼ – placebo (95% CI [1-sided p-value†])
TLC and FRC	Respreeza®▼ (92)	−1.50 (0.22)	0.62 (−0.02–1.26 [p = 0.029])
	Placebo (85)	−2.12 (0.24)	
TLC	Respreeza®▼ (92)	−1.45 (0.23)	0.74 (0.06–1.42 [p = 0.017])
	Placebo (85)	−2.19 (0.25)	
FRC	Respreeza®▼ (92)	−1.55 (0.24)	0.48 (−0.22–1.18 [p = 0.090])
	Placebo (85)	−2.02 (0.26)	

*Lung density was measured as the lung-volume adjusted15th percentile of the frequency histogram of the lung pixels assessed by computed tomography scan.
CI: confidence interval; FRC: functional residual capacity; n: number of subjects who had at least one computed tomography scan available; SE: standard error; TLC: total lung capacity
†A 1-sided p-value less than 0.025 and a positive estimate of the treatment difference of Respreeza®▼ minus placebo (i.e. the lower bound of the 95% CI being greater than zero) were taken to indicate superiority of Respreeza®▼ compared to placebo[3].

3.2 Open-label extension study (CE1226_3001)

A total of 140 subjects from the RAPID study were entered into a two-year open-label, single-arm, multicentre, multinational study[3,10]. In this extension study 76 subjects who had been treated with Respreeza®▼ (Early Start group) and 64 who had been treated with placebo (Delayed Start group) in the RAPID study received intravenous Respreeza®▼ (60 mg/kg) weekly for up to 2 years. An interim analysis using data from 50 Delayed Start and 47 Early Start subjects supported the results of the RAPID study. Delayed Start subjects had an annual rate of decline in lung density of −2.06 g/L/year when administered placebo which decreased to −1.31 g/L/year following Respreeza®▼ treatment. Early Start subjects had an annual rate of decline of −1.37 g/L/year during the double-blind portion of the study, which decreased to −1.08 g/L/year during the open-label portion (treatment years three and four) [3,10].

3.3 Safety

Safety data is available from the RAPID study, the open-label extension and four other studies (pharmacokinetic, dose-ranging, bioavailability, biochemical efficacy and safety studies). These data included 221 subjects in the Respreeza®▼ treated group and 87 subjects in the placebo group[2,3]. Despite different treatment durations in different groups and only a single arm in the open-label extension study, which caused some uncertainty in the figures, the Committee for Medicinal Products for Human Use (CHMP) considered that the rates of adverse reactions appeared to be similar in Respreeza®▼and placebo groups and that the safety profile of Respreeza®▼ is as expected from an A1-PI product[3]. Rates of serious treatment-emergent adverse events (TEAEs) were also similar in the treatment and placebo groups and no specific concerns were raised for severe adverse reactions or death. The main safety concern with human A1-PI is the risk of hypersensitivity; this was reported in both groups but with a similar incidence. There was no indication of viral transmission or development of A1-PI antibodies[3]. In the RAPID study one patient in the Respreeza®▼ group withdrew due to a TEAE (back pain) while four patients in the placebo group experienced TEAEs that led to withdrawal[1,10]. In the RAPID study the most common TEAE in the Respreeza®▼ group, reported in 40% of patients, was headache, but this was similar to the incidence in the placebo group (38%)[10].

3.4 AWTTC critique

- A1-PI deficiency is a rare genetic disorder with a prevalence of 1 in 2,500–5,000 in Western European newborns[3]. Patients with particular genotypes, most notably PiZZ, have increased risk of developing emphysema which is currently treated in the UK with BSC[1,5]. Treatment with Respreeza®▼ would be in addition to BSC.
- Enzyme replacement therapy in A1-PI deficiency has been used for almost two decades in the US, Canada and some European countries[3,11]. Respreeza®▼ is the first augmentation product licensed in the UK for the treatment of emphysema due to A1-PI deficiency[1].
- The primary endpoint in the pivotal studies was loss of lung density as measured by CT scan. Whilst it is not clear how lung density decline rate translates into clinical effect, CT densitometry has been accepted by the CHMP as a method for detecting emphysema progression in A1-PI deficient patients[3]. The CHMP also consider that it is not possible to address this uncertainty through feasible clinical studies due to the high variability of clinical outcome measures[3].
- In the RAPID study, treatment with Respreeza®▼ only resulted in a significantly slower annual rate of decline of lung density when measuring TLC alone. However, CHMP agreed that TLC alone is the most suitable endpoint to use in studies as it has the best possibility to detect small differences in lung density[1,3]. The CHMP were satisfied that the near significant efficacy results in the TLC/FRC combined analysis with the support of the significant result in the TLC only analysis supported evidence of effect, i.e. a reduction of the rate of lung density decline following Respreeza®▼ treatment in patients with A1-PI deficiency[3].
- In the RAPID and open-label extension studies the effectiveness of Respreeza®▼was measured using lung CT scans. However, in clinical practice CT scans are not regularly performed in patients with A1-PI deficiency. A1-PI deficiency is a life-long condition and progression of emphysema in these patients is slow. The company suggest that in practice the effectiveness of Respreeza®▼ would be evident over the long-term when measured by other parameters such as FEV_1 and DL_{CO}[1]. The RAPID study failed to demonstrate an effect on secondary endpoints, including FEV_1 or DL_{CO}; however, the study was not powered to do so due to sample size and duration. CHMP also noted that no restrictions were

placed on concomitant respiratory medication and the Respreeza®▼ group likely had more severe disease at baseline[3].

- The licensed indication does not define severe A1-PI deficiency or progressive lung disease. However, in the company submission it is stated that Respreeza®▼ should be initiated in patients meeting a number of criteria, in order to help define the licensed indication. AWTTC are of the opinion that these criteria broadly align with the inclusion criteria for the RAPID study, with the exception that patients in the RAPID study were not required to have rapidly declining lung function or lung density decline.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a cost-utility analysis (CUA) of Respreeza®▼ administered at a dose 60 mg/kg by once-weekly infusion for maintenance treatment to slow the progression of emphysema in adults who meet all of the following criteria:

- Diagnosis of severe A1-PI deficiency (< 11 μM)
- Genotypes PiZZ, PiZ(null) or Pi(null,null)
- FEV_1/FVC < 0.7 (indicating moderate airways obstruction) or emphysema demonstrated by 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 [DL_{co}]) or lung density decline (measured by emphysema on CT scan)

At the time of writing, no other A1-PIs treating the underlying cause of emphysema due to severe A1-PI deficiency are licensed in the UK. The comparator is therefore BSC for COPD that usually involves inhaled therapy with combinations of bronchodilators and corticosteroids, and in later stages home oxygen therapy or lung transplantation.

A Markov model with an NHS perspective is used to assess the cost-effectiveness of Respreeza®▼ compared to BSC. Patients enter the model at an age of 53 years in one of six health states which are defined by lung density decline status (no, slow or rapid) and FEV_1 predicted (> 50% or < 50%). Lung density decline status is defined as 0 g/l/year (no decline), 0–2 g/l/year (slow decline) and > 2 g/l/year (rapid decline) according to UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) registry data[12] for patients with A1-PI deficiency.

After each model cycle, patient lung density decline status can improve (transition to lower severity), remain the same, or worsen through the no decline, slow decline and rapid lung decline health states. Patients can also stay at the same FEV_1 level or worsen, but cannot improve FEV_1 state. Patients in the FEV_1 < 50% state can undergo lung transplantation if their lung function is declining and move to the transplantation state before entering the "post-transplant state". At any point, patients can die from A1-PI deficiency-related causes. The mortality risk depends on patient age and increased mortality is assumed for patients undergoing lung transplantation. All-cause mortality is applied as captured in the ADAPT registry. The model adopts a lifetime horizon to accommodate the entire patient pathway and 3.5% discounting is applied to both costs and benefits.

Clinical outcome data were derived from the pivotal randomised, double-blind, placebo-controlled, multi-centre RAPID study[10] that followed 180 patients for two years (with an optional extension of a further two years). Lung density decline rate was extrapolated from the study to the lifetime horizon while transition probabilities between FEV_1 states were derived from a UK registry for A1-PI deficiency patients (the ADAPT[13] and published data). These were then combined to give transition probabilities between the different health states of the model. Mortality data were taken from the study for the first two years in the BSC arm and the first four years in the Respreeza®▼ arm. Mortality rates beyond this point were derived from the UK registry and were stratified according to FEV_1 level and lung density decline status. No adverse events were included in the model[14]. The probability of receiving a lung transplant for patients with slow or rapid lung density decline under the age of 65 years was based on actual numbers of transplants in England[15,16] and published survival rates following transplant[17,18].

Patient quality of life was not measured in the pivotal RAPID study. Utility values for the different health states were therefore taken from the ADAPT registry and weighted according to FEV_1 level. Quality of life after lung transplant was taken from a published Dutch study[19]. Quality of life was assumed to be driven entirely by FEV_1 level; no effect of lung density decline on quality of life was included in the model due to lack of available data.

Costs captured by the model include Respreeza®▼ acquisition costs, administration costs, disease management costs and costs of lung transplantation and subsequent follow-up. Acquisition cost was provided by the company based on an average patient weight of 75.9 kg as observed in the RAPID study. Administration cost was based on 30 minute district nurse contact and costed using published unit costs[20,21]. Costs of disease management were derived from published evidence of COPD patients stratified and weighted according to FEV_1 status[22]. Cost of lung transplantation included assessment costs, donor acquisition costs, costs of the transplant and inpatient follow-up care as well as on-going monitoring and immunosuppressive treatment and was taken from published sources[23]. All costs were inflated to 2016.

Extensive deterministic and probabilistic sensitivity analyses are undertaken to assess parameter uncertainty. Scenario analyses are used to explore the effect changes in quality of life and costs for different lung density decline status, exclusion of lung transplant, alternative data sources and extrapolation techniques as well as different patient subgroups on the results.

4.1.2 Results

The results of the base case analysis are presented in Table 2. The incremental cost of Respreeza®▼ compared to BSC over a patient's lifetime (starting at age 53 years) is £433,938 with an incremental gain of 1.57 quality-adjusted life-years (QALYs) and 2.18 life years. The corresponding incremental cost-effectiveness ratios are £277,183 per QALY gained and £199,218 per life year gained. Furthermore, the model estimates that 29.3% of A1-PI patients would undergo lung transplantation compared to 21.7% in the BSC arm.

Table 2. Results of the base case analysis

Base-case analysis	Respreeza®▼	BSC	Difference
Total undiscounted cost (£)	579,274	65,245	514,029
Treatment undiscounted costs (£) Administration undiscounted costs (£) Disease management undiscounted (£) Lung transplant undiscounted costs (£)	479,614 12,644 21,365 65,650	0 0 16,247 48,997	479,614 12,644 5,118 16,653
Total discounted cost (£)	482,389	48,452	433,938
Total discounted life-years	10.05	7.87	2.18
Total undiscounted QALYs	10.01	7.64	2.37
FEV_1 ≥ 50% undiscounted QALYs FEV_1 < 50% undiscounted QALYs Lung transplant undiscounted QALYs	2.61 3.01 4.40	2.22 2.13 3.29	0.39 0.88 1.11
Total discounted QALYs	7.39	5.82	1.57
ICER (cost/QALY gained)	£277,183		
Probability cost-effective at £20,000 per QALY gained	0%		
Probability cost-effective at £30,000 per QALY gained	0%		
BSC: best supportive care; FEV_1: forced expiratory volume in one second; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio			

Table 3 summarises the scenarios provided by the company in order to address uncertainty around the key input parameters. Incremental cost-effectiveness ratios (ICERs) lie between £181,157 and £387,403 in all scenarios. Respreeza®▼ appears to be more cost-effective in patients with more progressive disease compared to patients with FEV_1 > 50%.

Table 3. Results of the scenario analyses

Scenarios	ICER	Plausibility
Scenario 1: Patients with no decline in lung density have utilities 20% greater than slow lung density decline patients and have 20% lower costs, whilst for patients with a rapid decline in lung density, the parameters are 20% in the reverse.	£246,950	This scenario is plausible. Clinical experts and data from the ADAPT registry have suggested that slow decliners would be expected to incur lower costs and experience improved quality of life, whilst rapid decliners would be expected to demonstrate the reverse - higher costs and lower quality of life.
Scenario 2: No discount applied to outcomes	£183,078	This scenario is implausible as discounting costs but not discounting health outcomes would artificially inflate the effectiveness of the intervention compared to the costs.
Scenario 3: Gomertz function used to fit survival curves	£281,656	This scenario is plausible as the Gomertz function was the second best fit for the survival data after the Weibull function used in the base case.
Scenario 4: Lung transplant health state excluded from the model.	£387,403	This scenario is implausible as it excludes the positive effect of Respreeza®▼ on lung transplantation and thus underestimates the cost-effectiveness of the intervention.
Scenario 5: Applying the survival probabilities based on RAPID study results	£181,157	As the RAPID study was underpowered and of too short duration to adequately capture the long-term effect of Respreeza®▼ on mortality, the plausibility of this scenario is uncertain.
Scenario 6: Treating early stage patients only (FEV_1 > 50%)	£302,237	The plausibility of this scenario is uncertain as the licensed indication does not specify a FEV_1 value or range.
Scenario 7: Treating later stage patients only (FEV_1 < 50%)	£224,679	The plausibility of this scenario is uncertain as the licensed indication does not specify a FEV_1 value or range.
Scenario 8: Treating patients with FEV_1 < 50% and a rapid decline of lung density only	£220,505	The plausibility of this scenario is uncertain as the licensed indication does not specify a FEV_1 value or range.
ICER: incremental cost-effectiveness ratio; FEV_1: forced expiratory volume in one second.		

The results of the deterministic sensitivity analyses indicate that the ICER is sensitive to the discount rates, patient weight (and thus treatment cost), the FEV_1 < 50% rapid lung density decline survival curve and the utility values of patients with an FEV_1 < 50% as well as mortality rates in the first four years. Results were also moderately sensitive to parameters relating to lung transplants. Results were insensitive to transitions between FEV_1 states, survival probabilities after year one, other survival curves and all costs. ICERs in all one-way sensitivity analyses ranged from £183,078 to £355,697 per QALY gained.

Probabilistic sensitivity analysis, based around the assumptions of the base case analysis, suggests a probability of being cost-effective at a £20,000 and £30,000 per QALY threshold of 0%.

4.1.3 AWTTC critique

The results of the base case CUA indicate that the use of Respreeza®▼ is considerably more costly but produces increased quality of life and as such has an ICER of £277,183 per QALY gained compared to BSC.

Strengths of the economic analysis:

- In the absence of other licensed treatments for the indication in question, BSC appears to be the appropriate comparator in patients with severe A1-PI deficiency.
- The model used to calculate cost-effectiveness seems robust and complete with clearly presented and well-structured calculations and worksheets.
- The company provides a detailed and transparent account of all methods and results.
- The company uses extensive sensitivity analyses to assess the effect of parameter uncertainty on the results.

Limitations of the economic analysis:

- The company states that the pivotal RAPID study was underpowered and follow-up was not long enough to detect effects on FEV_1 predicted and as such potential effects of Respreeza®▼ on FEV_1 are not captured in the model.
- The company appreciates that extrapolation of the RAPID study results to a lifetime horizon would introduce considerable bias and has used alternative UK registry data to supplement beyond two years in the placebo arm and four years in the intervention arm (RAPID extension). While this is justified, the direct comparison of different patient populations and BSC treatments will introduce bias.
- The model appears to assume sustained efficacy of Respreeza®▼ over a patient's lifetime. While the RAPID extension study provides outcome data for up to four years follow-up, there is no longer term data to support this assumption.
- The RAPID study was not powered to detect significant changes in mortality. Mortality rates beyond the study duration were obtained from ADAPT registry patients and extrapolated based on FEV_1 and lung density decline status. While this appears to be the best available data for this rare disease, the extrapolation might introduce bias. Furthermore, [commercial in confidence text removed] which might underestimate the cost-effectiveness of Respreeza®▼.
- Patients in the Respreeza®▼ intervention group in the RAPID study had slightly more advanced disease at baseline compared to the placebo group. This difference was not statistically significant but might lead to underestimation of the treatment effect of Respreeza®▼, especially as baseline data of the placebo arm was used to determine the distribution of patients in both model arms across the different health states at the start of the model.
- Due to the lack of available data, the model assumes that patient quality of life is solely determined by FEV_1 status. [commercial in confidence text removed]. Based on this evidence and the clinical expectation that a decline in lung density will reduce quality of life, the company consider it highly likely that lung density decline will have an effect on patient quality of life, in which case the model would underestimate the cost-effectiveness of Respreeza®▼.
- Due to the lack of available data, the model assumes that no increased costs are associated with increasing lung density decline. The company suggests that patients with rapid decline will be more likely to require more intensive monitoring and management which would result in cost savings in the intervention arm and in an underestimation of the cost-effectiveness of Respreeza®▼.
- Due to the lack of A1-PI deficiency specific data, costs of disease management were taken from a retrospective cohort study of 58,589 COPD patients in the UK[22].

The company states that this assumption is appropriate as emphysema is classed as COPD. However, patients in the COPD cohort are older (69.5 years vs. 53.8 years in the RAPID study), it includes 33.1% smokers (which were excluded in RAPID) and mean FEV_1 predicted values are higher (60.0% as opposed to 47.5% in the RAPID study). It is therefore uncertain how accurately the general COPD costs reflect the true costs of A1-PI deficiency.

- Adverse events were not included in the model. While this could introduce bias, the company suggests that adverse events of Respreeza®▼ were mild to moderate and similar to placebo and did not require extensive or costly treatment.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-utility of Respreeza®▼ for the treatment of patients with severe A1-PI deficiency.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Local registry (ADAPT) data in England reports that 540 patients have A1-PI deficiency and would be eligible for treatment with Respreeza®▼ with a prevalence of 1 in 100,000. Extrapolated to the Welsh population of 3,092,000[24] this would calculate to 31 patients in Wales. Based on Irish data (adjusted to Welsh population size), the company estimates that 5 new patients per year would become eligible for treatment. Treatment discontinuation rates are taken from the cost-effectiveness model, and assume that 6.8% of patients discontinue due to undergoing a lung transplant and that 5.08% die every year. The eligible population is thus 32 patients in year one increasing to 35 patients in year five. As there is no other treatment for the condition to date, the company estimates that uptake will be high with 50% of patients receiving Respreeza®▼ in year one, 70% in year two and 90% thereafter resulting in 16 patients being treated in year one increasing to 32 patients in year five.

Based on an average patient weight of 75.9 kg[10] and a weekly dose of 60 mg/kg, treatment costs amount to £57,200 per patient. Administration costs (30 minutes for a district nurse) are calculated to be £1,508, amounting to an annual cost per patient of £58,708.

The company provides a series of deterministic sensitivity analyses by increasing and decreasing all input parameters (except the dose and cost of Respreeza®▼) by 20%.

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 4. The company estimates that the budget impact of Respreeza®▼ will be £936,851 in year one, increasing to £1,870,995 in year five with a total budget impact over five years of £7,785,046.

Table 4. Company-reported costs associated with use of Respreeza®▼

	2017	2018	2019	2020	2021
Number of eligible patients (Patients with severe A1-PI deficiency)	31	32	33	34	35
Number of new patients becoming eligible for treatment	5	5	5	5	5
Number of deaths	2	2	2	2	2
Discontinue due to lung transplant	2	2	2	3	3
Total number of patients eligible	32	33	34	35	35
Estimated uptake	50%	70%	90%	90%	90%
Patients treated with Respreeza®▼	16	23	30	31	32
Medicine expenditure	£912,787	£1,319,553	£1,743,944	£1,785,857	£1,822,935
Savings from displaced medicines	0	0	0	0	0
Administration and monitoring costs	£24,064	£34,788	£45,977	£47,082	£48,059
Net financial costs	£936,851	£1,354,341	£1,789,921	£1,832,938	£1,870,995
A1-PI: Alpha1-proteinase inhibitor					

The estimated budget impact was found to be most sensitive to changes in the population, patient weight and prevalence of A1-PI deficiency (20%, 19% and 12% change, respectively). Changes to the remaining parameters had a minor influence in the estimated budget impact (< 10% change). In all sensitivity analyses, the estimated budget impact remained between £6,228,036 and £9,342,055 over five years.

5.1.3 AWTTC critique

Strengths of the budget impact analysis:

- The budget impact model presented is well-constructed, robust and complete.
- The company has used best available data for most parameters and made reasonable assumptions where no data was available.
- The company presents a range of one-way sensitivity analyses to account for uncertainty in the estimated budget impact.

Limitations of the budget impact analysis:

- The company uses population estimates from 2014 to calculate the prevalence of A1-PI deficiency despite there being more recent data available. While this will introduce bias, the impact on the budget impact is likely to be small.
- The annual incidence of newly eligible patients is based on Irish data which are extrapolated to the Welsh population. This could introduce bias and a survey of UK experts may provide more accurate estimates.
- Uptake rates are estimates by the company and changes in uptake will affect the budget impact. However, the company has not provided sensitivity analysis for this parameter.

5.2 Comparative unit costs

Annual acquisition costs of Respreeza®▼ are described in Table 5. No other treatment options are licensed in the UK for the specific treatment of patients with severe A1-PI deficiency to date.

Table 5. Examples of acquisition costs of specific treatment for patients with emphysema due to severe A1-PI deficiency

Regimens	Example doses	Approximate annual costs
Human alpha1-proteinase inhibitor (Respreeza®▼) 1000 mg vials	60 mg/kg once-weekly infusion (to be continued until death or lung transplant)	£57,200 (assuming mean weight of patient of 75.9 kg)
No other regimens are licensed for use in this patient population. Costs provided by company, including wastage. Costs of administration are not included.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, human alpha1-proteinase inhibitor (Respreeza®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 28 June 2016
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company suggests that Respreeza®▼ in the given population meets the AWMSG criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted European Medicines Agency (EMA) designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[25].

Whilst Respreeza®▼ has not been designated as an orphan medicine by the EMA, AWMSG will apply the same process and principles of consideration to a medicine developed specifically to treat an equivalent size population irrespective of whether it is designated by the EMA as an orphan medicine. The prevalence of the genotype associated with severe A1-PI deficiency in the UK is estimated to be between 1 in 1,600 and 1 in 5,000 newborns[26]. However, Respreeza®▼ is only licensed for the treatment of adults with severe A1-PI deficiency and evidence of progressive lung disease. Applying data from a UK registry for patients with A1-PI deficiency (ADAPT), it is estimated that up to 540 patients in England have A1-PI deficiency with clinically significant disease and may be eligible for treatment with Respreeza®▼. These data extrapolate to a prevalence of 1 in 100,000 people and therefore 31 patients in Wales[15].

AWTTC consider human alpha1-proteinase inhibitor (Respreeza®▼) eligible to be appraised as a medicine developed specifically to treat rare diseases. Should NMG/AWMSG consider that the orphan and ultra-orphan medicines and medicines specifically developed for rare diseases policy applies to Respreeza®▼, the criteria for assessing clinical effectiveness and cost-effectiveness will be the same as those applied to other medicines, but recognising that the evidence base may be weaker. NMG/AWMSG will consider evidence on the following to inform their decisions (see Table 6).

Table 6. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG.

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	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 BSC, and a median survival age of 58.3 years according to the model results presented by the company[27]. Patients with emphysema generally experience significant limitations in daily activities and reduced quality of life; quality of life was found to be lower in patients with emphysema associated with A1-PI deficiency compared with COPD[28].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	Respreeza®▼ is the first treatment for A1-PI deficiency licensed in the UK. Current standard care involves only symptomatic treatment and does not address the underlying disease.
Whether the medicine can reverse, rather than stabilise the condition.	Respreeza®▼ slows the progression of emphysema in adults with severe A1-PI deficiency, which has the potential to delay the need for lung transplantation. The mean decline in lung density over the two-year pivotal study was reduced by 34% compared to placebo. Furthermore, 3–8% of patients with initial slow decline in lung density (0–2 g/L/year) had no change or an increase in lung density the following year compared to 0% in the placebo group. However, the company states that this will not translate to a clinical improvement because the increase is only in non-functional tissue rather than functional tissue and that Respreeza®▼ stabilises or slows disease progression, but does not reverse or cure.
Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy), and that this “definitive” therapy is currently in development.	There is no evidence that Respreeza®▼ bridges the gap to curative therapy. However, more patients in the intervention group underwent lung transplantation compared to placebo (29.7% vs. 21.8%) according to the model results.
The innovative nature of the medicine.	Respreeza®▼ is the only available disease-modifying treatment for A1-PI deficiency in the UK. However, alternative A1-PI replacement therapies are available elsewhere globally and other specific evidence demonstrating innovation has not been presented.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	There is evidence from the RAPID study that Respreeza®▼ slows lung density decline by 34%[3] and according to a company model extends patients’ life by three years[1]. The company suggests that this will enable patients to remain in full-time employment for longer, therefore prolonging their independence. Also, treatment has the potential to delay the need for lung transplantation which could result in reduced distress and fatigue for the patient[1].
Added value to the patient’s family (e.g. impact on a carer or family life).	The company suggests that the decrease in respiratory decline will stabilise the number of clinic visits, hospitalisation episodes and delay in the need for oxygen supplementation and lung transplantation which will have a positive impact on burden and psychological distress of family and carers. However, these positive effects have not been quantified.
NMG: New Medicines Group; AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; BSC: best supportive care; A1-PI: Alpha1-proteinase inhibitor; QALY: quality-adjusted life-year	

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