



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1530 – Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease

Applicant: National Blood Authority (NBA)

Date of MSAC consideration: MSAC 74th Meeting, 22-23 November 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting National Product List (NPL) blood product listing of purified human alpha1-proteinase inhibitor (A1-PI) for the treatment of A1-PI deficiency, leading to chronic obstructive pulmonary disease (COPD), was received from the National Blood Authority (NBA) by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support A1-PI for the treatment of A1-PI deficiency. MSAC recognised the large unmet clinical need and the evidence of a radiologically detectable treatment effect, but was concerned with the weak evidentiary basis provided to suggest that changes in CT density predicts clinically meaningful health outcomes. MSAC also advised that, even with favourable assumptions regarding estimates of possible health outcomes of A1-PI treatment, the economic evaluation generated unacceptably large incremental cost-effectiveness ratios at the prices proposed by the sponsors.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted the impact that severe A1-PI deficiency (serum A1 \leq 11 μ M), with emphysema (FEV₁<80%), has on patients and their carers, resulting in strong consumer support for the proposed treatment both in Australia and overseas.

The proposed treatment is lifelong intravenous blood augmentation therapy via weekly infusions of purified human A1-PI for ex- or never-smoking patients. MSAC noted that the two alternative products are considered to be essentially bioequivalent. MSAC noted that the recommended dosing is 60mg/kg per week, but that there are ongoing clinical trials investigating optimal dosing regimens, with dosing up to 120mg/kg per week. MSAC noted that if the required dose is higher, the overall cost would increase if the current price per mg is maintained.

MSAC noted that augmentation therapy with A1-PI is not currently funded or reimbursed in private or public settings in Australia for this or any other clinical indication.

MSAC noted the estimated prevalence of carriers of alleles related to A1-PI deficiency in the Australian population is 1 in 8.9 individuals. The PiZZ allele (with a prevalence of 1 in 5584), contributes to the greatest burden; however, not all people with PiZZ A1-PI deficiency will go on to develop severe emphysema. MSAC noted that the estimated number of people meeting the criteria for treatment with A1-PI in Australia in 2018 was **redacted**. Treatment is lifelong and not curative; therefore, the number of patients being treated is expected to moderately cumulative increase over time.

MSAC noted that the comparator intervention for patients with severe A1-PI deficiency and emphysema is best supportive care (BSC).

MSAC noted that, overall, it appears that A1-PI is safe, with most adverse events being related to the underlying disease.

MSAC noted that there are no statistically significant differences between A1-PI and placebo in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (St. George's Respiratory Questionnaire), respiratory function (FEV₁), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (D_{LCO}).

MSAC noted that the only statistically significant difference observed in clinical trials was for CT-measured lung density, which favoured A1-PI therapy compared with placebo. MSAC noted that recommending public funding of A1-PI products requires accepting that effects on CT-measured lung density have been demonstrated to be a surrogate for effects on outcomes known to be clinically meaningful, including respiratory function, quality of life, overall survival, or quality-adjusted life-years (QALYs). However, even the clinical significance of the observed difference in CT-measured lung density is uncertain, as minimal clinically important differences (MCIDs) for changes in this surrogate have not been established in the peer-reviewed literature.

MSAC noted the claim that A1-PI therapy meets three of the four criteria warranting Rule of Rescue. However, it is unclear whether CT-measured lung density is a sufficiently informative surrogate for the Rule of Rescue criterion of 'worthwhile clinical improvement'.

MSAC noted that CT lung density calculations are not routinely performed in Australia, although it is likely all modern scanners could be equipped to do so with access to necessary software (noting that the cost of software is unknown).

A1-PI is known to be ineffective in smokers. Strict requirements would therefore be needed to ensure use is limited to non-smokers (of tobacco and/or cannabis).

MSAC noted that the treatment cost with A1-PI is high (approximately **\$redacted** per patient per year) for the patient's lifetime and the base case modelled incremental cost-effectiveness ratio (ICER) is more than \$200,000 per QALY gained using a weighted average price for the two available A1-PI therapies. MSAC advised that this ICER/QALY was unacceptably large and based on assumptions of long-term clinical effect that favoured the intervention, and substantial price reductions would be required to bring it within an acceptable range.

MSAC noted that the assessment group attempted to improve the modelled cost-effectiveness of the A1-PI products by applying an evidence-based stopping rule for patients who demonstrate limited treatment response to A1-PI therapy. In the model, 113/1,000 individuals in the cohort progress from no decline or slow decline to rapid decline, despite being on A1-

PI therapy for four years – the A1-PI therapy costs for these individuals beyond four years was then removed from the model. However, this was only associated with a modest improvement in cost-effectiveness and the ICER remained unacceptably large (more than \$200,000/QALY compared with more than \$200,000/QALY for the base case).

MSAC also noted that an additional univariate sensitivity analysis (performed by the assessment group by changing specific transitions from FEV₁ >50 to FEV₁ <50 to remove a modelled treatment effect on FEV₁ which contradicted the results of the randomised trials) did not have a major impact on the ICER. If both A1-PI therapy and BSC arms had FEV₁ annual probability declines of **redacted**%, then the ICER would increase from more than \$200,000/QALY to more than \$200,000/QALY.

MSAC noted that there is significant uncertainty regarding the number of patients who will be diagnosed with A1-PI deficiency if the A1-PI products are available on the NPL. The NBA would need to be able to negotiate an overall risk sharing arrangement with suppliers to mitigate this financial risk.

MSAC concluded that there is a clear physiological effect on lung density which is detectable radiologically; however, there is no basis on which to draw a large clinical effect, and thus no evidence of patient-relevant outcomes.

MSAC again acknowledged the high priority the public consultation feedback gave to meeting the clinical need that the applicant claims will be helped by this intervention, but considered that the evidence was inadequate to justify the therapeutic claims made in the application.

4. Background

Augmentation therapy with any A1-PI therapy is not currently funded or reimbursed in private or public settings in Australia (for this or any other clinical indication).

5. Prerequisites to implementation of any funding advice

PROLASTIN-C and Zemaira (marketed as Respreeza in Europe), are two augmentation therapy products registered on the Australian Register of Therapeutic Goods (ARTG) in Australia. The two therapies consist of the same components with slightly different eligibility criteria (Table 1).

Table 1 Approved augmentation therapies and their indications

Product	ARTG ID and details
PROLASTIN-C	ARTG ID 234553: indicated to increase serum A1-PI levels in adults with congenital deficiency of alpha-1 anti-trypsin and with <u>clinically significant emphysema (FEV₁ less than 80%)</u> . The data for clinical efficacy of PROLASTIN-C is derived from changes in the biomarkers alpha-1 anti-protease level and CT lung density. Efficacy on FEV ₁ or patient relevant endpoints such as quality of life or pulmonary exacerbations has not been established in randomised clinical trials. Clinical trials have only included <u>patients who were not smoking</u> .
Zemaira	ARTG ID 273182: indicated for maintenance treatment, to slow the progression of emphysema in adults with documented <u>severe A1-PI deficiency (A1-PI less than 11 µM)</u> and <u>progressive lung disease</u> . Patients are to be under <u>optimal pharmacologic and non-pharmacologic treatment</u> .

Abbreviations: ARTG = Australian Register of Therapeutic Goods, FEV₁ = forced expiratory volume in 1 second, µM = micromolar.

6. Proposal for public funding

Augmentation therapy with A1-PI is proposed for reimbursement on the NPL, managed by the NBA. As such, no Medicare Benefits Schedule item descriptor is required.

7. Summary of public consultation feedback/consumer issues

Six associations provided targeted feedback, and one individual provided non-targeted feedback on this consultation. All respondents using the feedback form ‘strongly agreed’ with the clinical claim made by the applicant and argued the urgent priority to address the unmet clinical need.

8. Proposed intervention’s place in clinical management

The population to be considered in this assessment is ex- or never-smoking patients with emphysema (defined as $FEV_1 < 80\%$) and severe A1-PI deficiency (defined as serum A1 levels $\leq 11 \mu\text{M}$ (approximately 59 mg/dL); Hatipoglu and Stoller 2016).

Patients with A1-PI deficiency are currently managed with best supportive care (BSC). BSC includes pharmacological strategies (e.g. inhaled medications) and non-pharmacological strategies (e.g. pulmonary rehabilitation and physical activity) aimed at providing symptomatic relief. The current (Figure 1) and proposed (

Figure 2) clinical management algorithms are presented below.

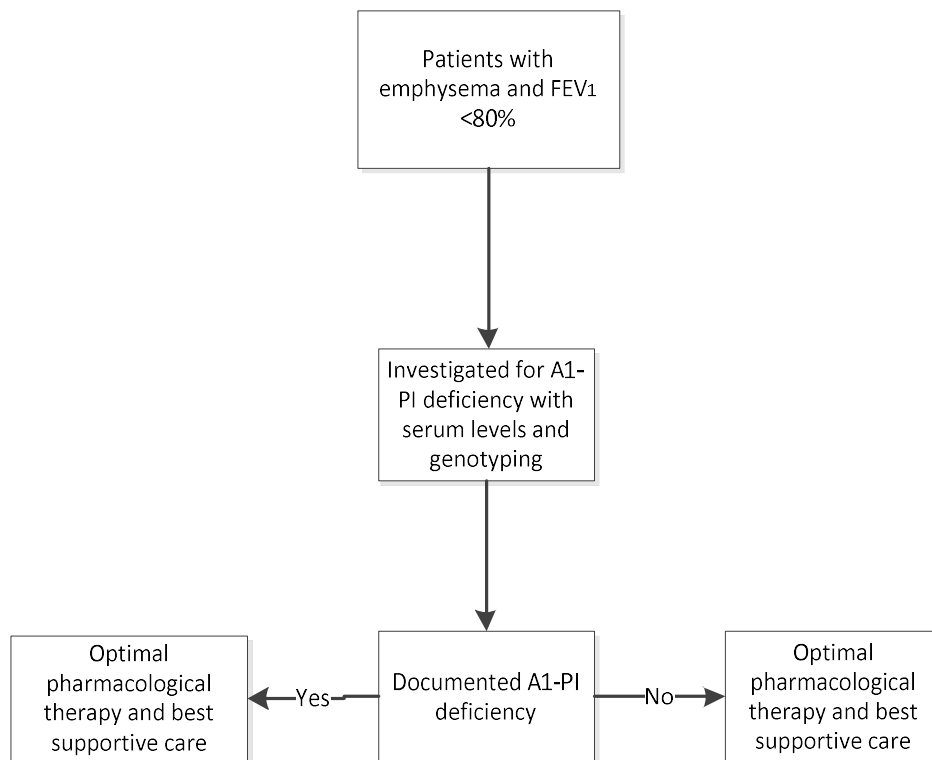


Figure 1 Current clinical management algorithm for patients with emphysema and FEV₁ <80%

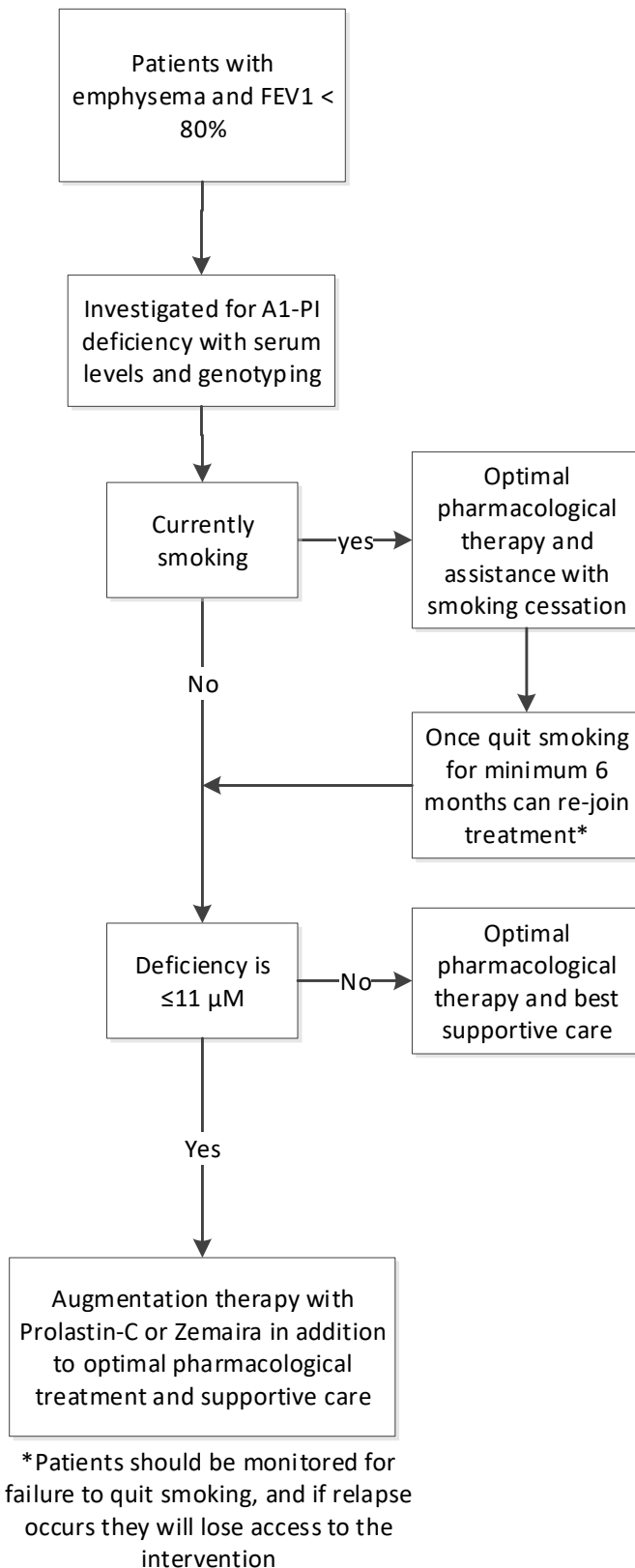


Figure 2 Proposed clinical management algorithm for patients with emphysema and FEV1 <80%

9. Comparator

The application stated that there are currently no active comparators for augmentation therapy that modify the progression of emphysema or COPD in patients with A1-PI deficiency. The comparator for patients with COPD is BSC.

10. Comparative safety

The application stated that three randomised controlled trials (RCT)s were identified that evaluated the effectiveness of A1-PI compared to placebo (n=313). Included patients were relatively homogenous across the included studies, representing ex- or never-smokers with severe A1-PI deficiency (serum A1 $\leq 11 \mu\text{M}$) and emphysema (forced expiratory volume in 1 second (FEV₁) 25% to 80%). The included RCTs were generally well conducted; however, the method of allocation concealment was poorly reported across all trials. Seventeen single-arm studies were identified that provided evidence on the safety of A1-PI. Key safety outcomes were: death due to adverse events, severe adverse events, and discontinuation or hospitalisation due to adverse events.

The application stated that six deaths occurred in the eligible studies, which included a total of 899 patients. None of these deaths was reported to be treatment-related. Severe adverse events were also uncommon, with a median occurrence of 2% in the patient population (range 0%-38%). Discontinuation due to adverse events had a median occurrence of 0.5% in the patient population (range 0%-12%) across nine studies. Hospitalisation had a median occurrence of 1.5% in the patient population (range 0%-14%) across four studies.

The application stated that three studies reported safety in patients treated with one of the two therapies under assessment, Zemaira and PROLASTIN-C. All of these studies found that rates of severe adverse events were unchanged across intervention groups (Figure 3).

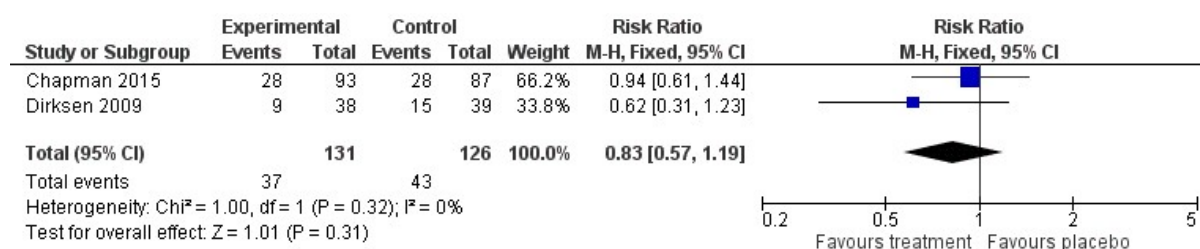


Figure 3 Forest plot indicating the pooled rate of severe adverse events for A1-PI compared to placebo

The application stated that fifteen studies reported any adverse event, with a rate ranging from 0% to 100% and a median of 37%. Differences between the RCTs and observational studies in the rates of any adverse event may indicate under-reporting in the observational studies. Dyspnoea and treatment-related adverse events were also reported. Dyspnoea occurred after augmentation therapy in 12.5% of the patient population (range 0%-35%). Events reported by the authors to be treatment-related had a median occurrence of 11% in the patient population (range 0%-38%).

The application stated that overall, it appears that the intervention is safe, with most events being related to the underlying disease.

11. Comparative effectiveness

CT-measured lung density was the primary outcome in two RCTs, and FEV₁ was the primary outcome in one RCT.

No significant differences between A1-PI and placebo were identified in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (St. George's Respiratory Questionnaire), respiratory function (FEV₁), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (DLCO). No relevant data were identified for dyspnoea.

The only statistically significant difference observed was for CT-measured lung density (Figure 4), which favoured A1-PI. However, the clinical significance of this difference is

uncertain, as MCIDs for changes in CT-measured lung density have not been established in the peer-reviewed literature.

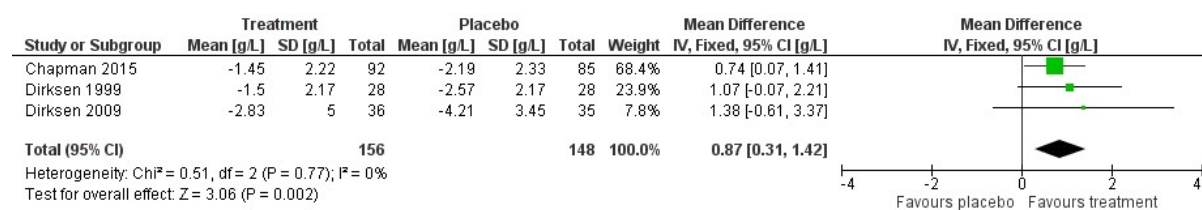


Figure 4 Forest plot indicating changes in CT-measured lung density (g/mL) in A1-PI compared to placebo measured at 24 to 30 months follow-up. (Chapman 2015 and Dirksen 1999 reported an annualised rate, whereas Dirksen 2009 reported the change from baseline at 24 months.)

The summary of findings (incorporating both benefits and harms) is shown in

Table 2.

Table 2 Balance of clinical benefits and harms of A1-PI relative to placebo as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Risk with placebo	Risk with A1-PI (95% CI)	Relative effect (95% CI)	Participants (studies)	Quality of evidence (GRADE)	Comments
Mortality F/U 24 months	34 per 1,000	12 per 1,000 (2 to 78)	RR 0.35 (0.05 to 2.27)	180 (1 RCT)	⊕⊕⊕⊖ MODERATE	Uncertain due to low event rate, RR subject to error
Quality of life (SGRQ) F/U 24 to 30 months	-	MD 0.83 points lower (3.49 points lower to 1.82 points higher)	-	248 (2 RCT)	⊕⊕⊖⊖ LOW	Direction favours placebo; not statistically significant
Annual exacerbation rate F/U 24 to 30 months	-	-	Higher reported RR (1.26, 95% CI 0.92 to 1.74), MD (0.36, 95% CI -0.44 to 1.16) in A1-PI group	257 (2 RCT)	⊕⊕⊕⊖ MODERATE	Direction favours placebo; not statistically significant
CT-measured lung density F/U 24 to 30 months	-	SMD 0.87 g/L higher (0.31 higher to 1.42 higher)	-	304 (3 RCT)	⊕⊕⊕⊕ HIGH	Direction favours A1-PI; statistically significant
Mortality due to treatment-related adverse events F/U 24 months	No treatment-related deaths reported			180 (1 RCT)	⊕⊕⊕⊖ MODERATE	No reported deaths due to treatment-related adverse events
Severe adverse events F/U 24 to 30 months	341 per 1,000	283 per 1,000 (195 to 406)	RR 0.83 (0.57 to 1.19)	257 (2 RCT)	⊕⊕⊕⊕ HIGH	Direction favours A1-PI; not statistically significant
Discontinuation due to adverse events F/U 24 to 30 months	48 per 1,000	10 per 1,000 (2 to 62)	RR 0.22 (0.04 to 1.30)	248 (2 RCT)	⊕⊕⊕⊖ MODERATE	Direction favours A1-PI; not statistically significant
Hospitalisation due to adverse events F/U 3 to 6 years	Median rate 1.4% (range 0.0% to 14.3%)			497 (4 observational studies)	⊕⊕⊖⊖ LOW	-

Abbreviations: F/U = follow-up, MD = mean difference, RR = relative risk, SGRQ = St George's Respiratory Questionnaire, SMD = standardised mean difference.

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Clinical claim

The clinical claim is that, relative to best supportive care, A1-PI (with either product) slows disease progression in patients with severe A1-PI deficiency and emphysema. On the basis of the evidence presented, the contracted assessment stated that A1-PI therapy has uncertain effectiveness relative to best supportive care, and that relative to placebo, there appear to be no important differences in safety outcomes associated with A1-PI therapy.

12. Economic evaluation

A cost-utility analysis was undertaken to determine the value of A1-PI in addition to optimal pharmacological treatment and supportive care (best supportive care).

Table 3 Summary of the economic evaluation

Perspective	This economic evaluation was conducted from the perspective of the Australian health system. It includes resource use supported by government and patients, along with health outcomes applicable to the treatment of patients with emphysema due to A1-PI deficiency.
Intervention	Augmentation therapy in addition to optimal pharmacological treatment and supportive care.
Comparator	Best supportive care: optimal pharmacological treatment and supportive care
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RAPID study, RAPID-OLE study, UK Registry data
Time horizon	30-year time horizon in the base case Sensitivity analyses include a time horizon of 20 years and 40 years
Outcomes	Quality-adjusted life years (QALYs) gained and life-years gained
Methods used to generate results	Cohort expected value analysis
Health states	1. FEV ₁ ≥ 50% predicted, no lung density decline 2. FEV ₁ ≥ 50% predicted, slow lung density decline 3. FEV ₁ ≥ 50% predicted, rapid lung density decline 4. FEV ₁ < 50% predicted, no lung density decline 5. FEV ₁ < 50% predicted, slow lung density decline 6. FEV ₁ < 50% predicted, rapid lung density decline 7. Lung transplant 8. Dead
Cycle length	1 year
Discount rate	5% used for base and 3.5% and 7% sensitivity analyses
Software packages used	Microsoft Excel 2010

Using a weighted average price for the two A1-PI products, the modelled incremental cost-effectiveness ratio (ICER) of A1-PI in addition to BSC (relative to BSC alone) was found to be more than \$200,000 per QALY over a time horizon of 30 years. Adopting a modelled time horizon equivalent to the trial duration (four years) yielded an ICER of more than \$200,000 per QALY (Table 4).

Table 4 Incremental cost-effectiveness ratio (1,000-patient cohort)

	Cost (AU\$)	Incremental cost (AU\$)	Effectiveness (QALYs)	Incremental effectiveness	ICER (AU\$)
Trial period					
A1PI augmentation therapy	Redacted	Redacted	Redacted	Redacted	more than \$200,000
Best supportive care	Redacted		Redacted		
Lifetime					
A1PI augmentation therapy	Redacted	Redacted	Redacted	Redacted	more than \$200,000
Best supportive care	Redacted		Redacted		

Abbreviations: A1PI = Alpha-1 proteinase inhibitor; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The assessment noted that the price paid for the augmentation therapy product is the key driver of model results (Table 5).

Table 5 Drivers of the economic model

Description	Method/Value	Impact
Cost of the AT product	The average dosing for augmentation therapy is taken from the RAPID trial and applied to an average weight of 75.9 kg. The number of vials (rounded to a whole number) is multiplied by average, high and low AT product prices.	The base cost of augmentation therapy assumes a price per 1,000 ml (\$redacted). This varies from \$redacted to \$redacted per 1,000ml vial. The estimated ICER varies considerably between more than \$200,000 and more than \$200,000 per QALY.
Transition between FEV ₁ and CT density decline during RAPID drives clinical benefit	There were considerable differences in transition between health states for the augmentation therapy and BSC arms in the RAPID trials. The economic model assumes movement to no, slow and rapid decline tracks during the trial period is sustained for a lifetime.	A higher number of patients move to the FEV ₁ <50 decline states on the BSC arm in RAPID. Movement during the trial period drives economic results. Allowing transition between no, slow and rapid tracks after 4 years has limited impact on the estimated ICER.
Selection of extrapolation model for the FEV ₁ <50 rapid-decline group survival	In most cases the Gompertz model is the best fit model to extrapolate survival and this model is used across all non-transplant states. The model is varied as part of sensitivity analyses that included use of the Log-logistic, Lognormal, Weibull, Exponential and Generalised Gamma specifications. Large numbers of patients transition to this state during the trial period, particularly on the BSC arm.	The specification of the FEV ₁ <50 rapid-decline model had the largest impact on the estimated ICER. The use of Lognormal, Generalised Gamma and Weibull models resulted in the ICER being 10% more cost effective, while use of the Exponential model resulted in a 10% decrease in cost effectiveness.
Disease management costs for COPD	Disease management costs in many reviewed COPD economic models were an aggregate of maintenance and acute care costs during flare ups. The frequency of flare ups was not explicitly modelled in this assessment. The Thomas et al. 2014 analysis included acute care proportions for each state. They are varied by 20% for each COPD state.	This variation has limited impact as economic results are governed by AT product costs. The proportion of severe COPD patients who are very severe, assumed to be 74% in the base cases, also varied. Similarly, this scenario had limited impact on the estimated ICER.

Abbreviations: BSC = best supportive care, COPD = chronic obstructive pulmonary disease, CT = computed tomography, FEV₁ = forced expiratory volume in 1 second, ICER = incremental cost effectiveness ratio.

13. Financial/budgetary impacts

The financial impact of the potential listing of A1-PI augmentation therapy is calculated using an epidemiological approach over a five-year period, based on an estimate of the number of patients eligible for treatment.

Table 6 Estimated financial impact to government from augmentation therapy listing

	2019	2020	2021	2022	2023
Total government costs					
AT patients	Redacted	Redacted	Redacted	Redacted	Redacted
NBA-supported AT product costs	Redacted	Redacted	Redacted	Redacted	Redacted
MBS-supported infusion service delivery	Redacted	Redacted	Redacted	Redacted	Redacted
Total net costs to governments	Redacted	Redacted	Redacted	Redacted	Redacted

Abbreviations: AT = augmentation therapy, MBS = Medical Benefit Schedule, NBA = National Blood Authority.

A key uncertainty is the price of augmentation therapy. Variations in price have a large impact on both financial and economic attractiveness because of the large contribution of the augmentation therapy itself to overall resource in the economic model. The proposed price of PROLASTIN-C is **\$redacted** per 1,000ml vial and ZEMAIRA **\$redacted**. An average price of **\$redacted** is included, with **\$redacted** and **\$redacted** used as high and low bounds in

sensitivity analyses. Varying the prevalence proportions by 10% has a lesser financial impact. Uptake rate also has an impact. A decrease in year 2022 uptake from 90% to 80% results in a **\$redacted** budget requirement in that year. MSAC noted that the financial estimates were sensitive to assumptions regarding rates of diagnosis of A1-PI deficiency and non-smoking rates. MSAC noted advice from the product manufacturers in their pre-MSAC responses that patients receiving A1-PI are highly motivated to maintain their non-smoking status.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Rarity or under-diagnosis of condition in Australia	Alpha1-proteinase inhibitor (A1-PI) deficiency appears to be underdiagnosed in the USA, which means it could also be the case in Australia. The population may therefore be much larger than the estimated redacted patients.
Safety	Overall, it appears that the intervention is relatively safe compared to placebo, in addition to best supported care.
Effectiveness	The only statistically significant difference observed was for CT-measured lung density, which favoured A1-PI therapy compared to placebo; however, the clinical significance of this difference is uncertain, as MCIDs for changes in CT-measured lung density have not been established in the peer-reviewed literature. No significant differences between A1-PI and placebo were identified in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, quality of life (SGRQ), respiratory function (FEV ₁), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (DLCO).
Costs	Not all relevant costs were captured (e.g. additional A1-PI serum tests, additional IgA tests, IV device, additional consultations).
Population	Trials included patients with a wide range of lung function.
Rule of Rescue	It is claimed that A1-PI deficiency meets three of the four criteria warranting the Rule of Rescue. It is unclear whether CT-measured lung density is a sufficiently informative surrogate for judging the Rule of Rescue criterion of ‘worthwhile clinical improvement’.
Potential bias	The small pool of researchers and the low frequency of investigator-initiated trials mean there is potential for selection and/or reporting bias.

ESC discussion

The request is for lifelong intravenous blood augmentation therapy via weekly infusions of purified human A1-PI (60 mg/kg per week) for the treatment of A1-PI deficiency, also known as alpha-1 antitrypsin deficiency (AATD). ESC noted that ongoing trials are investigating optimal dosing regimens (including higher doses). ESC noted the manufacturers’ claim that successful listing of the blood product in the target population and setting will lead to slower disease progression compared to best supportive care.

ESC noted that A1-PI deficiency is an inherited genetic condition that results in decreased circulating, and/or abnormally functioning, A1-PI protein. Severe A1-PI deficiency (defined as serum levels of A1-PI $\leq 11 \mu\text{M}$) most commonly manifests as emphysema or liver disease.

Prevalence data in Australia are limited. The prevalence of the PiZZ (protease inhibitor, homozygote Z) allele in Australia, which is identified in the most severely affected patients (with greatly increased risk of emphysema), is estimated at 1 in 5,584. The prevalence of PiSZ, which is identified in individuals who produce less A1-PI than normal (and have an increased risk of emphysema), is estimated at 1 in 841. ESC noted that it is the PiZZ allele that contributes to the greatest burden of lung disease in the A1-PI deficient population, but not all people with PiZZ A1-PI deficiency go on to develop severe emphysema.

ESC noted that the intended population comprises ex-smokers or patients who have never smoked, who have emphysema and severe A1-PI deficiency (serum A1-PI $\leq 11 \mu\text{M}$). ESC noted that the contracted assessment estimated that the number of people meeting the criteria for treatment with A1-PI in Australia in 2018 was likely to be **redacted**. Considering treatment is lifelong and not curative, the number of patients being treated is expected to have a moderate cumulative increase over time. However, ESC noted that A1-PI appears to be under-diagnosed in the USA, which means it could also be the case in Australia. ESC noted that there are estimated 80,000–100,000 patients with severe A1-PI deficiency in the USA (Stoller et al.; *UpToDate*).

A1-PI augmentation therapy is an intervention that can be added to BSC for patients with emphysema. ESC noted clinical advice received during the assessment that emphasised the necessity for patients to maintain a non-smoking status for this augmentation therapy to be effective.

ESC noted that 17 single-arm studies were included for the evaluation of safety outcomes. Overall, it appears that the intervention is safe, with most observed events judged as being related to the underlying disease. ESC noted that patients with an IgA deficiency are at risk of an anaphylactic reaction.

ESC noted that no studies comparing A1-PI augmentation therapy to optimal pharmacological treatment and supportive care were identified. ESC noted that, because of the rarity of A1-PI deficiency, clinical trials are often underpowered to detect statistical differences in outcomes (such as quality of life and mortality). The key studies of A1-PI therapy have used CT-measured lung density (PD15; 15th percentile lung density) as a primary outcome. It is claimed that CT-measured lung density correlates to markers of lung health and mortality, and this correlation has been used to infer clinical efficacy. PD15 has been validated as a consistent measure of lung density, specifically in A1-PI deficient patients, in order to overcome the challenges of adequately powering a study to detect significant differences in functional outcomes (such as FEV₁) (Parr et al. 2006; Schluchter et al. 2000). However, ESC noted that minimum clinically important differences (MCID) in CT-measured lung density for predicting changes in disease progression have not yet been defined in the peer-reviewed literature.

ESC noted that three randomised controlled trials (RCTs) were identified (RAPID, EXACTLE and DIRKSEN99) that evaluated the effectiveness of A1-PI therapy compared to placebo in 313 patients. The studies included ex-smokers or patients who have never smoked, with severe A1-PI deficiency (serum A1-PI $\leq 11 \mu\text{M}$) and a range of emphysema severity (FEV₁ [forced expiratory volume in 1 second] 25% to 80%). ESC noted that different primary outcome measures were defined by the investigators: the RAPID and EXACTLE trials used CT-measured lung density, while the DIRKSEN99 trial used FEV₁. ESC noted that, at 24–30 months, no significant differences between A1-PI augmentation therapy and placebo were identified across these RCTs in relation to mortality, exacerbation of chronic obstructive pulmonary disease (COPD), hospitalisation due to COPD exacerbation, quality of life (St George's Respiratory Questionnaire; SGRQ), respiratory

function (FEV₁), exercise capacity (incremental shuttle walk test) or carbon monoxide diffusion capacity (DLCO). No relevant data were identified for dyspnoea as a measure of respiratory function, or the BODE index (BMI, obstruction, dyspnoea, exercise capacity).

The only statistically significant difference observed was for CT-measured lung density, which favoured A1-PI therapy. However, ESC noted that the clinical significance of this difference is uncertain, as MCIDs for changes in CT-measured lung density have not been established in the peer-reviewed literature. However, ESC noted a recent American Thoracic Society conference abstract that has proposed an MCID threshold of -2.89 g/L (95% CI: $-2.59, -3.25$; Crossley et al 2018). In this context, one of the product manufacturers stated that “based on the annual preservation of lung tissue (0.74 g/L/year) demonstrated in the RAPID trial in favour of A1-PI therapy, the proposed MCID would be achieved within 3.9 years as compared to an untreated patient.”

ESC noted that the EXACTLE trial reported four methods for measuring CT-measured lung density. The assessment report used the 24-month data from the physiological adjustment method for comparability with the DIRKSEN99 and RAPID trials. ESC noted that a Cochrane review (Gotzsche and Johansen 2016), that included an average of the four methods, yielded almost identical results as the assessment meta-analysis, indicating concordance of the different methods.

ESC noted that the comparative effectiveness measured by FEV₁ (showing no statistically significant difference between A1-PI therapy and placebo) was also similar across the assessment meta-analysis and the Cochrane review.

ESC noted that 12 studies reported on the correlation between CT-measured lung density, and lung function measures (FEV₁, KCO gas transfer) and patient-relevant outcomes (mortality and quality of life). However, ESC noted confounding variables, such as differences in assessing lung density and lung zones, and that the reported correlations were largely cross-sectional rather than comparing changes in CT-measured lung density with changes in lung function measures over time. ESC noted a meta-analysis (Crossley et al.) reported a correlation between CT-measured lung density and FEV₁ and KCO gas transfer, although there was a high degree of heterogeneity across included studies.

ESC noted the conclusions of the Assessment Report that, overall, CT-measured lung density correlates with lung function measures (FEV₁ and K_{CO}) and mortality, but findings were inconsistent regarding correlations between CT-measured lung density and quality of life.

ESC noted the claim that A1-PI therapy meets three of the four criteria warranting Rule of Rescue. However, it is unclear whether CT-measured lung density is a sufficiently informative surrogate for the Rule of Rescue criterion of ‘worthwhile clinical improvement’.

ESC noted there is the potential for selection and/or reporting bias in this area of research, given the small pool of researchers and the low frequency of investigator-initiated trials.

ESC also noted an earlier meta-analysis (COPD 2009; 6(3):177-84) showed A1-PI augmentation therapy was associated with a 26% reduction in rate of FEV₁ decline (absolute difference 17.9 mL/year; 95% CI 9.6 to 26.1 mL/year) in a subset of patients with baseline FEV₁ of 30–65%. Similar trends were seen in patients with baseline FEV₁ of <30% or >65%, but they were not statistically significant. This 26% treatment effect was used to drive differences across the A1-PI therapy and BSC arms of the modelled economic evaluation.

ESC provided the following responses to key clinical policy issues:

- Regarding whether there is clinical evidence to support a recommendation for public funding of A1-PI products – ESC noted that this requires accepting that CT-measured lung density has been demonstrated to be a surrogate for outcomes known to be clinically meaningful.
- Regarding potential management criteria – ESC queried whether FEV₁ should be added to the proposed initial eligibility criteria as a more objective measure of emphysema severity. ESC noted that FEV₁ 25% to 80% reflected the eligibility criteria across the three identified RCTs, and queried whether this could form the basis for stipulating a suitable threshold.
- Regarding whether there is any material distinction between alpha-1 products currently registered in Australia (Prolastin-C and Zemaira), affecting clinical utility or price level – ESC noted evidence in the contracted assessment that demonstrated the two agents are bioequivalent, with 60 mg/kg once weekly regimens yielding equivalent changes in trough serum antigenic A1-PI levels. Neither product was found to be cost-effective at the prices currently proposed by the respective manufacturers.

ESC noted that the results of the modelled economic evaluation were presented in two steps. The first step outlined cost-effectiveness results for the trial period of four years. This length of follow-up reflects the maximum follow-up of the RAPID trial (Chapman et al. 2015) and the open-label extension study (RAPID-OLE) (McElvaney et al. 2017). An average hypothetical cohort of 1,000 patients progresses between FEV₁% and CT-measured lung density decline states based on results of the trial within a cohort-based semi-Markov model. Numerical differences in mortality across the A1-PI therapy and BSC arms were taken from the RAPID-OLE and RAPID studies for the first two and four years, respectively (McElvaney et al. 2017); (Chapman et al. 2015).

The efficacy benefit associated with treatment that leads to improvements in patient morbidity were captured in the model using RAPID trial data, with the primary analysis being expressed as the incremental cost per additional QALY gained. Resource use was attached to each state using proposed A1-PI maintenance therapy product costs and MBS item costs. Australian Refined Diagnosis Related Groups (AR-DRG) costs were applied to the frequency of GP and hospital presentations for UK COPD patients of differing severity (Thomas et al. 2014) to estimate disease management costs of A1-PI deficiency.

The second step involved extrapolating RAPID transition data over an additional 26 years (lifetime). It was assumed that transitions between health states with varying rates of CT-measured lung density decline occurred during the follow-up of the RAPID and RAPID-OLE studies and that patients stayed on no, slow or rapid decline tracks for the remaining 26 years. The patient-level data on which the post hoc linear regression analyses were based were provided to the Assessment Group by the manufacturer that sponsored the RAPID and RAPID OLE studies.

Mortality data for the remainder of the model's lifelong time-horizon were based on observations from 10 years of followed-up patients in the UK AATD registry. A number of parametric models were fitted to the UK registry data by the Assessment Group to extrapolate observational data for the lifetime projections.

ESC noted that a range of sensitivity analyses were undertaken to test the robustness of the results of the modelled economic evaluation. This included changes in baseline distributions of individuals with emphysema or COPD stratified according to extent of airflow obstruction, and being mild, moderate, or severe.

ESC noted that most models for COPD health states are stratified by FEV₁. However, given that CT-measured lung density was the primary outcome in the RAPID trial, the model also incorporated FEV₁ to define the health states in the model as well as three levels of predicted decline in CT-measured lung density (none, slow or rapid decline) as a driver for mortality. Patients could move from FEV₁>50% to FEV₁<50% health states, but not the other way around.

ESC noted clinical advice provided to the Assessment Group that, for the extrapolation after 4 years, the rate of CT-measured lung density decline in A1-PI patients stabilises. Accordingly, the model assumed that, after the first 4 years of the modelling timeframe, patients would remain in the no, slow or rapid decline pathways for the remainder of the modelled timeframe.

In the pre-modelling studies undertaken by the Assessment Group to extrapolate overall survival from UK registry with follow-up to 10 years, the Gompertz function was found to have the best fit (lowest AIC statistic) across most subpopulations and, for consistency, was used in the base case for all subpopulations. ESC noted that, whilst this choice was reasonable, other extrapolation functions of this overall survival curve were more favourable for the intervention.

ESC noted that the model was driven by the larger number of patients who are retained in the FEV₁<50% slow decline state, as a result of augmentation therapy. Most incremental life years saved (LYS) and quality-adjusted life years (QALYs) accrue to the FEV₁<50% slow decline state from the FEV₁<50% rapid decline state.

ESC noted the economic model yielded base case results well above the threshold usually considered by MSAC to be acceptably cost-effective: with an ICER of more than \$200,000 per QALY for the trial period of 4 years, and an ICER of more than \$200,000 per QALY for the lifetime (30 year) model.

ESC noted that the incremental clinical benefit in the model accrues between 5 and 15 years (i.e. is driven by extrapolation of effects beyond the 4-year trial period). Sensitivity analyses showed that the cost of A1-PI product is the key driver of the economic model (accounting for **redacted**% of the cost). It is therefore uncertain what price would be acceptably cost-effective.

ESC noted that, even at the lowest proposed price of \$**redacted** per 1,000 mL of A1-PI therapy, the lifetime modelled ICER is more than \$200,000 per QALY. Unit prices that would generate ICERs within the range usually considered to be acceptable by MSAC are unlikely to be acceptable to the manufacturers. Consequently, ESC suggested the assessment group be asked to explore different 'continuation rule' scenarios, using the existing model structure, that are evidence-based and clinically feasible.

For example, what would the ICER impact be if A1-PI therapy was ceased after 4 years (the trial period), in patients who exhibit a rapid CT-measured lung density decline rate (for example >2.0 g/L) while on treatment? ESC noted this would require inclusion of CT-measured lung density scans (at a frequency that would need to be justified) to monitor response, and therefore need to be added to treatment costs in the model, while being removed from disease management costs (to avoid double-counting).

When looking at the financial/budgetary impacts, ESC noted that there is no direct estimate available for the number of Australian patients with COPD with A1-PI deficiency. Estimates were derived from the prevalence of COPD patients in Australia, the estimated prevalence of ZZ phenotypes in the USA (adjusted to reflect Australian ethnicities), and the rate of A1-PI

diagnosis using US data. ESC noted that if A1-PI augmentation therapy is funded on the NPL, current testing rates are likely to increase due to the availability of a treatment option.

ESC noted that the base case estimate of total costs to government was \$10 - \$20 million per year (2019–2023). ESC noted that these estimates are highly sensitive to the price of the products and were based on the weighted average of the price proposed by each of the two manufacturers.

ESC noted that the financial estimates were also sensitive to assumptions around diagnosis rates and assumptions regarding the proportion of non-smokers in otherwise potentially eligible patients, and that higher rates for both of these assumptions are plausible and could reasonably be expected to yield financial estimates 2–3 times higher than those presented as the base case.

ESC noted that the financial estimates are highly sensitive to:

- the price of A1-PI therapy;
- assumptions around the proportion of patients with COPD who are diagnosed as A1-PI-deficient; and
- the proportion of potentially eligible patients who are assumed to be non-smokers.

ESC suggested the assessment group also undertake additional sensitivity analyses of the financial estimates around the price of A1-PI therapy, that correspond directly to the ‘continuation rule’ scenarios explored in the economic model, noting that, for the scenario suggested above, this might require extending the timeframe of the financial analysis to 10 years so that the impact of therapy cessation after 4 years can be captured. If a ‘continuation rule’ is proposed, any additional MBS costs associated with implementing the rule (e.g. for CT-measured lung density scans, smoking status tests) would need to be captured in the revised financial estimates.

ESC noted that an issue was raised at PASC about whether Indigenous Australians might be discriminated against if treatment was stopped when a patient continues smoking. However, ESC noted that PASC had received clinical expert advice that this is a disease mainly affecting non-Indigenous Australians. It was noted that objective criteria would be needed for all patients receiving therapy, and that there is a significant opportunity cost for continuing A1-PI therapy in patients who smoke (as the treatment is rendered entirely ineffective by smoking).

ESC noted the following key economic and financial policy issues for MSAC:

- The prices proposed by manufacturers do not yield ICERs within the range that is typically considered to be acceptably cost-effective.
- There is uncertainty surrounding both the primary outcome measure (CT-measured lung density), and also its correlation with survival, which suggests post-listing data collection would be warranted – the Australian Patient Registry proposed by one of the companies, could facilitate this.
- The treatment is high cost (\$**redacted** per patient per year) for their lifetime, and known to be ineffective in smokers. Strict requirements would be needed to ensure use is limited to non-smokers.
- The potential role for other continuation rules for A1-PI therapy could be explored, e.g. in patients who are not or no longer responding to treatment (after an agreed duration of treatment, and according to pre-specified, objective criteria) – again, the proposed Australian Patient Registry could assist with this.

- The potential role for a Risk Sharing Agreement between the NBA and manufacturers could be explored to manage the real potential of under-estimation of diagnosis and treatment rates in the potentially eligible population.
- Public funding of A1-PI therapy may result in changes in management; for example, increased use of prior tests (i.e. capturing test-negative individuals as well as diagnosed individuals), use of tests to monitor compliance with smoking cessation, and use of tests to monitor response to A1-PI therapy. If MBS-funded, these impacts are not currently captured in the financial estimates.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

CSL Behring is disappointed MSAC did not support A1-PI replacement therapy for the treatment of A1-PI deficiency with COPD. A1-PI deficiency with COPD is a life-threatening and very rare condition, with no currently funded disease-modifying treatment alternatives. CSL Behring agrees with MSAC that there is a high unmet medical need for patients with A1-PI deficiency and strong consumer support for funded access, and is pleased that MSAC acknowledged the clear physiological effect of A1-PI therapy on lung density. CSL Behring maintains that the evidence supporting the benefit of A1-PI therapy is strong in the context of this rare and slowly progressive disease, noting that it is not feasible to collect survival outcome data in a clinical trial setting likely to be sufficient to satisfy MSAC's requirements in a timely manner. CSL Behring believes there is a strong basis for applying a broader decision-making framework in this context, beyond the conventional evaluation approach used in MSAC's consideration. CSL Behring remains committed to working with the National Blood Authority and Jurisdictional Blood Committee to continue to progress the application for timely funded treatment for Australian patients suffering from this devastating disease.

Grifols is disappointed with the decision by the Medical Services Advisory Committee (MSAC) not to support purified human alpha1-proteinase inhibitor (A1-PI) for the treatment of patients with A1-PI deficiency. Grifols is committed to working with the National Blood Authority and other relevant stakeholders, including clinicians and patient organisations, to ensure that this effective medicine, with a positive impact on survival, will be made available to those in need and who have the greatest capacity to benefit using appropriate mechanisms (e.g. Grifols' latest generation genetic tools, initiation and continuation criteria). Grifols welcomes the acknowledgement by MSAC's Evaluation Sub-Committee that A1-PI deficiency is a rare disease and that clinical trials for rare diseases are often underpowered to detect clinically significant outcomes. Furthermore, the company is keen to work through the cost-effectiveness, albeit acknowledging the current conventional framework is not well suited to treatments for rare diseases like A1-PI. Indeed, other factors, such as the current lack of clinically effective treatments, clinical need, seriousness of the disease, the rule of rescue, as well as access and affordability from the patient perspective, and comparatively small financial implications for Federal and State/Territory governments, should also be considered when assessing the social value of medicines to treat A1-PI.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)